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ABSTRACT

Provides information on cellular morphology and physiology, including general cell characteristics, the nucleus, ribosomes, endoplasmic reticulum, Golgi apparatus, lysosomes, mitochondria, microtubules, microfilaments, and membranes. Focuses on membranes which are postulated to play an important role in many aspects of health and disease. Highlights research studies and scientists associated with major discoveries in cellular biology. Includes a detailed glossary of terms used in this booklet. (CS)

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INSIDE THE CELL

The New Frontier of Medical Science

U S DEPARTMENT OF HEALTH,
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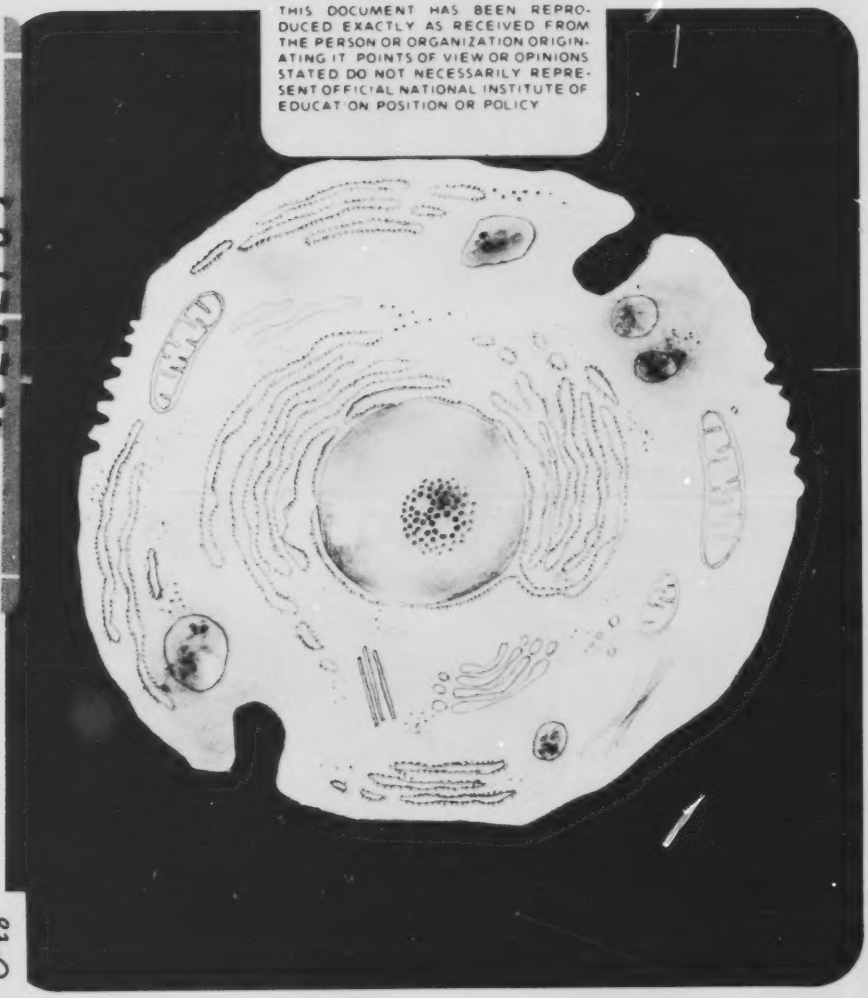

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Series: A New Medical Science for the 21st Century

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The National Institute of General Medical Sciences (NIGMS) is unique among the National Institutes of Health in that its main mission is the advancement of the basic medical sciences. It supports selected research and research training programs in areas that underlie all medical investigation, namely, cell and molecular biology and genetics. Ten of the scientists whom it supported have won Nobel Prizes since 1968 for their pioneering work on the structure and function of genetic material, the action of hormones, and the structure of the cell. Knowledge resulting from this work contributes directly to the progress of research in the other institutes of NIH. The Institute also develops and supports interdisciplinary studies in pharmacology, toxicology, anesthesiology, biomedical engineering, epidemiology, and trauma and burn research.

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The National Institute of General Medical Sciences (NIGMS)

INSIDE THE CELL

The New Frontier of Medical Science

By Maya Pines

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

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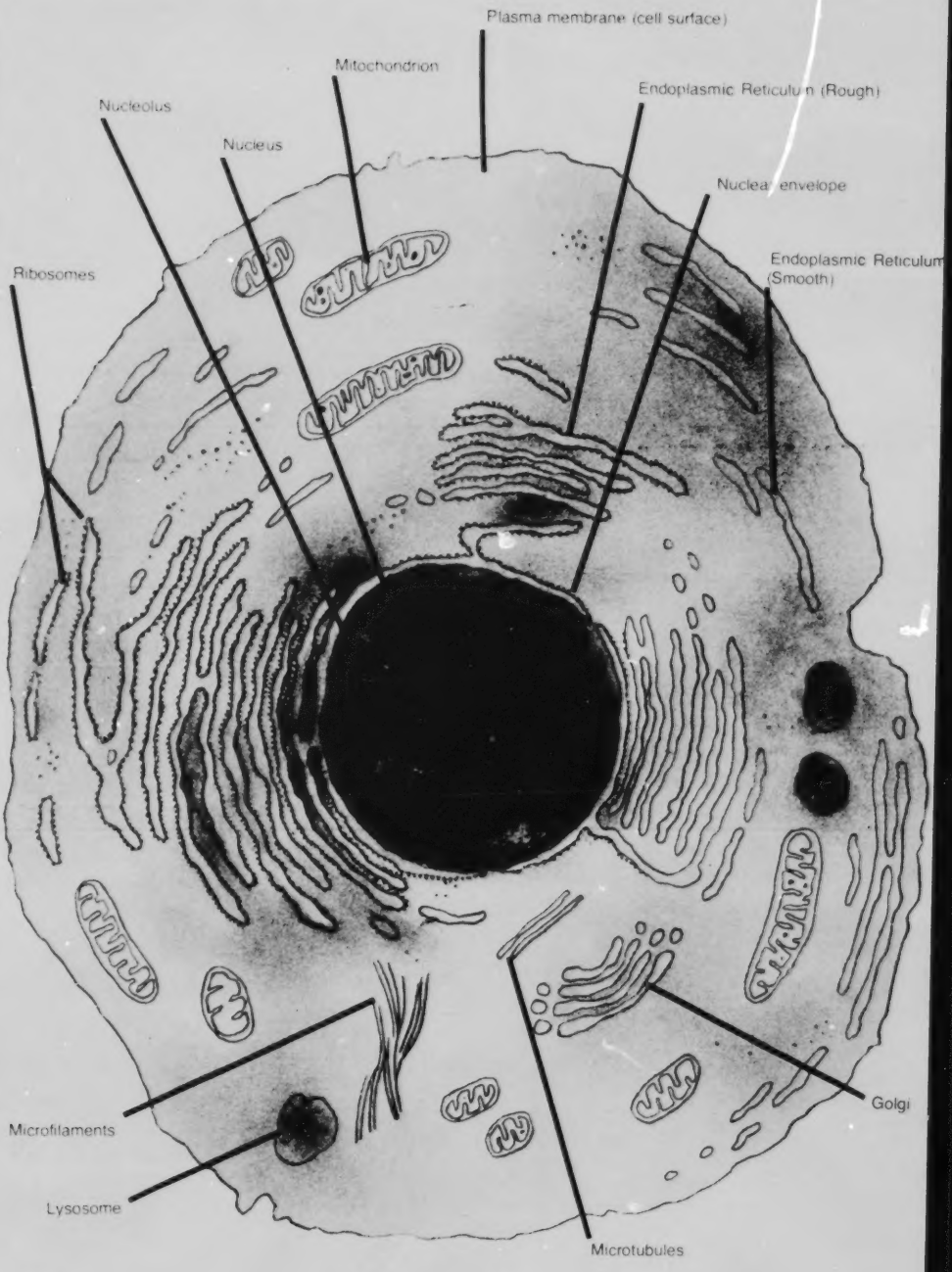

Each human cell has tiny organs (organelles) of its own which are as essential to the life of the cell as the heart, liver and brain are essential to the life of the body. This diagram of a typical mammalian cell shows the nucleus (which contains the genes) and major organelles.

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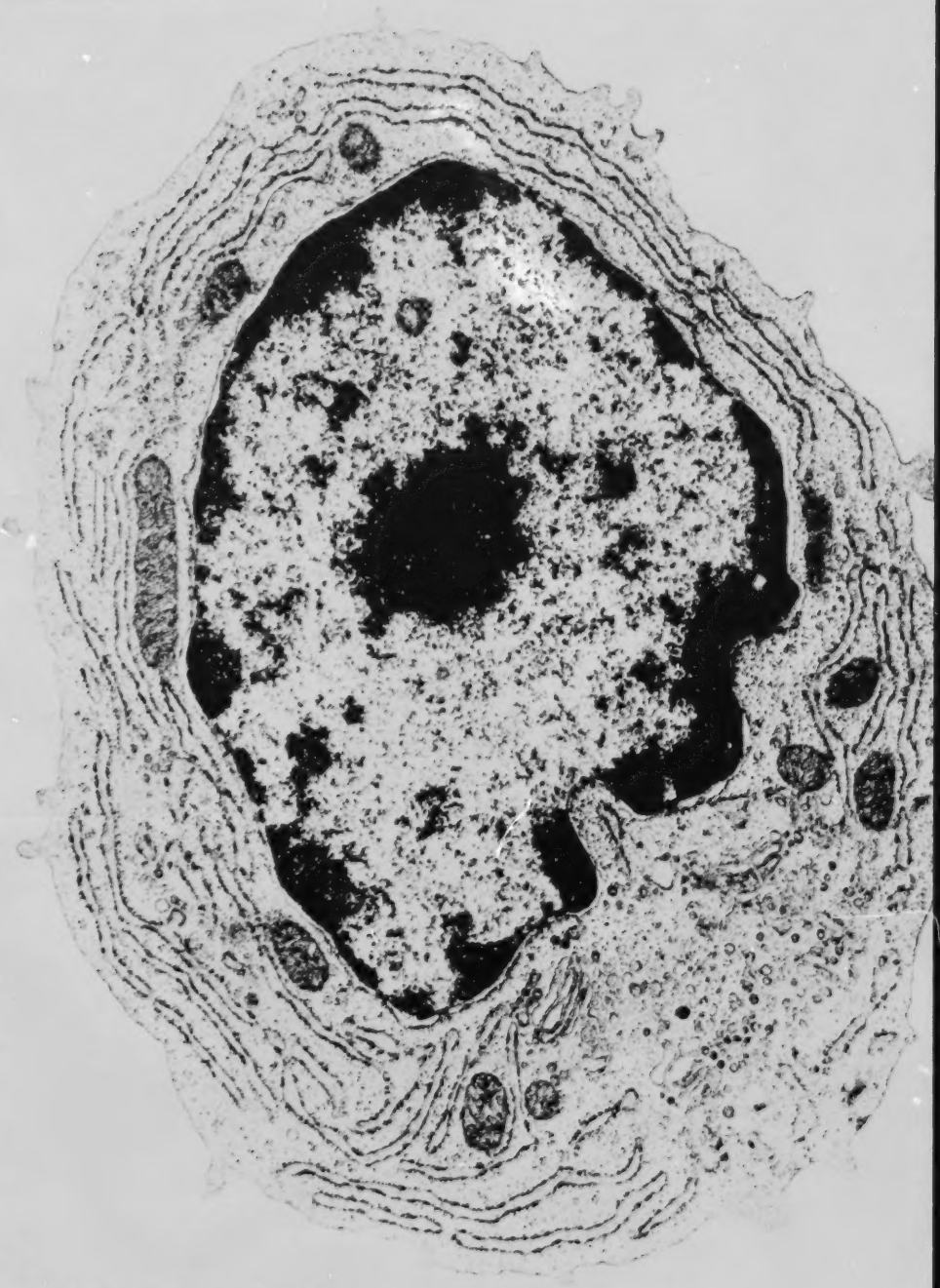
"We are sick because our cells are sick. We cannot make ourselves well unless we know what is happening inside our cells." **Christian de Duve, Rockefeller University.**



Magnified 21,000 times under an electron microscope, a rat's white blood cell reveals the double membrane around its nucleus, layers of endoplasmic reticulum, several mitochondria, and other organelles.

THE NEXT BIG LEAP

The next big leap in medical science depends largely on how fast and how well scientists succeed in understanding the activity of thousands of tiny organs in a new world which they have only recently begun to explore—the world of the living cell.

This miniature world holds the key to the major health problems of today: cancer, atherosclerosis, genetic diseases, diabetes, mental illness. It is no longer a matter of fighting bacteria or viruses, now that vaccines and antibiotics can prevent or cure so many infectious diseases. The illnesses that still defeat us are far more insidious, for they result from disorders within the human cell, the basic unit of the body. To control these, we need to know much more about what goes on inside the cell.

In the past 30 years, researchers have created a new field, modern cell biology. Through an ingenious combination of electron microscopy, biochemical separations and analyses of cell parts, X-ray crystallography and other means, they have revealed the cell as enormously complex and tightly organized—a strange, watery world in which diaphanous particles of various sizes and shapes float about, in rapid motion, engaged in thousands of chemical reactions. Each cell has its own power plants; its own digestive system; its own factories for making proteins and other essential molecules. Most important, it has an intricate communications network through which it can regulate its own activities (for example, "decide" when to reproduce) as well as receive messages from other cells, sense changes in its environment, and send out messages of its own.

The discovery of this teeming world within the cell and the study of its organization are leading scientists to develop some entirely new concepts of health and disease. Cancer, for instance, can now be viewed— and studied—as a derangement of the cell cycle. No matter what organ of the body is attacked by cancer, the disease always involves tissue whose cells have lost the ability to sense when they should stop multiplying. Normal cells stop reproducing upon contact with other cells, in a process called "contact inhibition." But cancer cells go right on growing and multiplying, even piling up in layers that become tumors, as if their surface membranes could no longer perceive signals from nearby cells. Instead of staying in the part of the body for which they were specialized, they often slide away and migrate to other parts of the body, to form new tumors. The control of cancer may well depend on unraveling these mechanisms.

Other incurable or chronic diseases may some day be related to defects of the cell's mitochondria, the curious, semi-independent little organs (organelles) in the cell which act as the cell's power plants. Mitochondria reproduce themselves with their own genetic material, and many scientists believe that they are descended from bacteria-like parasites which infected a primitive cell billions of years ago and then stayed on, in a useful symbiotic relationship with other parts of the cell. Without the energy produced by the mitochondria, cells could neither move nor synthesize the chemicals they need nor, in the case of muscle cells, fuel their contractions. The study of mitochondria may thus provide us with new ways of preventing or treating a wide variety of diseases —for example, certain diseases involving muscle cells.

Researchers are also beginning to zero in on the genetic factors which often play such an important role in disease. Many disorders of organelles are hereditary, since the information for making these organelles comes from the genes, the units of hereditary material which are found in the nuclei of cells. Some genetic diseases have

been traced to defects in a single gene. In many more diseases, however, including such widespread ones as diabetes, coronary heart disease and schizophrenia, several genes as well as various environmental factors appear to be involved.

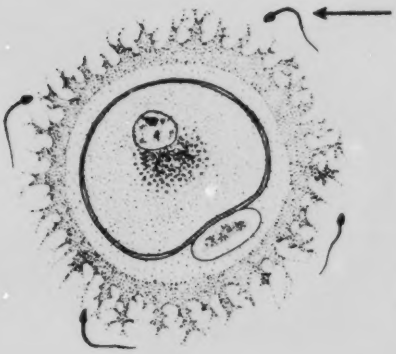
Despite all the new clues and the magnificent achievements of the last 30 years, scientists are only beginning to approach the stage where their research will have a major impact on human health. The cell used to be almost virgin territory. The pioneers of cell biology have succeeded in mapping out and analyzing its major features. But they are still very far from understanding the mechanisms which control the organelles' varied activities. They do not know, for example, what regulates the series of orderly changes involved in normal cell growth and development. It is one of the greatest mysteries in biology that although each human being starts life as a single cell, and each cell then divides into two identical cells, which divide again, somehow these cells differentiate in a highly ordered fashion so that some make an eye, some make hair, some make bone or blood, and others make nerves or skin tissue. How do these cells know what to do? Why do certain kinds of cells die, never to be replaced, while others go on reproducing? What happens to our cells—and to ourselves—as we age?

Vast amounts of information about the cell had to be accumulated before scientists could even attempt to study such questions. It is only now that such research on cell regulation is becoming possible.

This pamphlet will describe some of the discoveries that have brought us to this breath-taking stage, and then focus on one of the most exciting areas of current cell research: The study of the cell's ultra-thin but extraordinarily active surface membrane, which plays an important role in many aspects of health and disease. Much of this work is being supported by the Cellular and Molecular Basis of Disease Program of the National Institute of General Medical Sciences (NIGMS), which is part of the National Institutes of Health (NIH), Bethesda, Maryland.

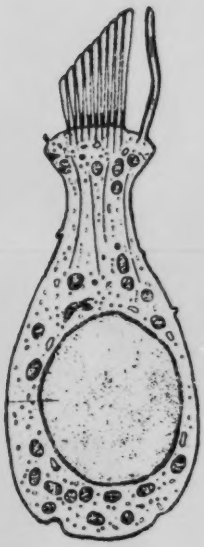
THE VARIETY OF HUMAN CELLS

Nerve cell



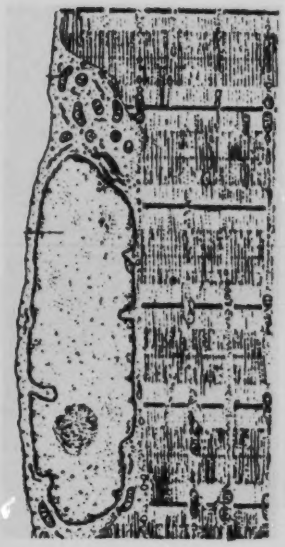
Egg cell

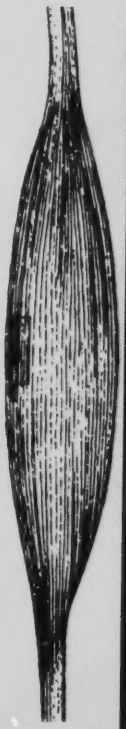
Sperm cell



Hair cell

Rod cell in eye





Muscle cell

The single cell with which we start life divides again and again into many kinds of specialized cells whose structure varies according to their function. Some nerve cell fibers extend over 3 feet in length to reach from spine to toe. The orderly structure of muscle cells is shown here in such detail that if the entire muscle cell were drawn on the same scale as this fragment, it might be 1,000 feet long.

WHAT ARE CELLS?

The idea that every human and animal body is made up of cells emerged with full force from an encounter between two German scientists in 1838. Nearly two centuries earlier, in 1665, the English physicist Robert Hooke had peered at a sliver of cork through a primitive microscope and noticed some "pores" or "cells" in it. But since these looked like cavities (they were actually the cell walls of dead cork tissue), they were believed to serve as containers for the "noble juices" or "fibrous threads" of plant life. Besides, such cells seemed to exist only in plant material.

During a dinner conversation in 1838, however, the botanist Matthias Schleiden, who had been studying plant cells, and the zoologist Theodor Schwann, who had been examining the nervous tissue of animals, suddenly realized that the similarities between the structures they had been investigating were too strong to be accidental. Eventually Schwann showed that *all* animal tissue is composed of cells, including bone, blood, skin, muscle, and glands. Even sperm and eggs are cells. The two men then developed the cell theory, which united plant and animal sciences by recognizing that the cell was the basic building block of all living organisms, from orchids and earthworms to human beings. It was a stunning intellectual achievement.

Within two decades, another German scientist, Rudolf Virchow, founded cellular pathology by showing that the immediate seat of most diseases is the cell.

But what was the cell?

Obviously there were big differences between, say, an

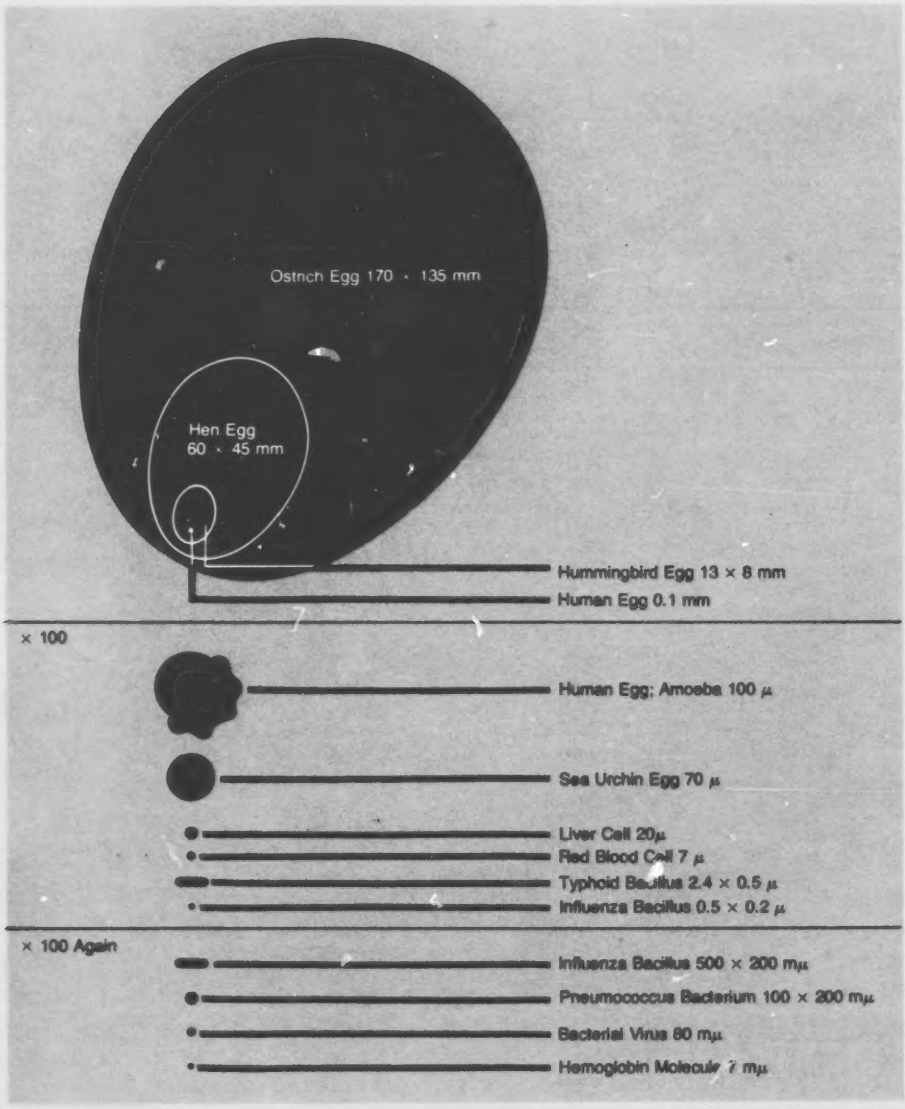
egg cell and a sperm cell. Muscle cells which could contract had to be quite different from liver or bone cells. Nerve cells had long, thin fibers which might extend more than 3 feet from the spinal cord to the toes, while blood cells had no fibers at all. Plant cells had a unique ability to use light for energy.

Then what did all these cells have in common? Their basic elements were surprisingly difficult to find. Despite the best efforts of scientists, the cell remained essentially a "black box" for more than a century after the development of the cell theory.

The cell was just a blob of jelly, or some primordial soup enclosed in a bag, thought the early microscopists. For this reason they named the substance "protoplasm," a word derived from the theological term for Adam, the first formed being, "protoplast." As their instruments improved, they noticed that every cell had a denser central area—a nucleus. But for a long time they could not find anything else in the surrounding jelly, which became known as "cytoplasm."

Eventually, with further improvements in lenses and staining techniques, they began to distinguish some other particles in the cell as well. These looked mostly like dots or strands. There was no way to study them in detail with a light microscope. No matter how hard they tried, researchers always came up against an insuperable obstacle: the wavelength of light.

With a light microscope—even one with perfect lenses and perfect illumination—one simply cannot distinguish objects that are smaller than one-half the size of the wavelength of light. Since white light has an average wavelength of 5,500 angstroms, half this size is 2,700 angstroms, or .27 micrometers. (One micrometer is one-thousandth of a millimeter, and there are about 25,000 micrometers to an inch). Any two lines that are closer together than .27 micrometers will be seen as a single line, and any object with a diameter smaller than .27 micrometers will be invisible—or, at best, show up as a blur.


Ostrich Egg 170 × 135 mm
Hen Egg
60 × 45 mm
Hummingbird Egg 13 × 8 mm
Human Egg 0.1 mm
× 100
Human Egg; Amoeba 100 μ
Sea Urchin Egg 70 μ
Liver Cell 20μ
Red Blood Cell 7 μ
Typhoid Bacillus 2.4 × 0.5 μ
Influenza Bacillus 0.5 × 0.2 μ
× 100 Again
Influenza Bacillus 500 × 200 mμ
Pneumococcus Bacterium 100 × 200 mμ
Bacterial Virus 80 mμ
Hemoglobin Molecule 7 mμ

Cell sizes: the largest living cells—the eggs of ostriches and other birds—are shown here at half their actual size, while the red blood cell is magnified 100 times and the pneumococcus bacterium is magnified 10,000 times.

Unit	Symbol	
Centimeter	cm	= 0.4 inch
Millimeter	mm	=0.1 cm
Micrometer (Micron)	μm (μ)	=0.001 mm
Nanometer (Millimicron)	nm (mμ)	=0.001μm
Angstrom unit	Å	=0.1 nm

Small, Smaller, Smallest—Units of Measure.

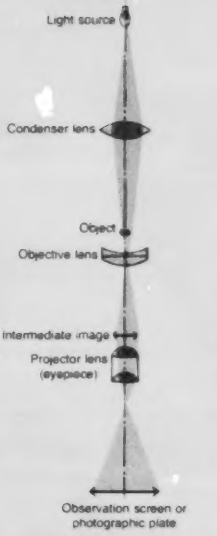
Many of the organelles *are* smaller than that. To enter the world of the cell is to make a voyage such as Alice made through the Looking Glass, where everything becomes smaller and smaller, and curiouser and curiouser. The average human being is made of some 100 trillion cells (100,000,000,000,000). Although these cells vary considerably in size, according to their function, on the average they are about 20 micrometers in diameter. In this scale of things, the cell's nucleus is relatively large: about 5 to 10 micrometers in diameter. But the other organelles vary from a width of only 1 micrometer to structures so fine that they must be measured in nanometers (which are 1,000 times smaller than micrometers), or even in angstrom units (10 times smaller than nanometers). To see such tiny particles under a microscope, one had to bypass light altogether and use a different sort of "illumination," one with a shorter wavelength.

A FRUITFUL FUSION OF TWO TECHNIQUES

The invention of the electron microscope in the 1930's filled the bill. Electrons can be accelerated in a vacuum until they reach a speed at which their wavelength is only .05 angstroms, one-hundred-thousandth that of white light. In the electron microscope, beams of these high-speed electrons are focused on a cell sample. As the electrons pass through the sample, different parts of the cell absorb or scatter them in different ways, to form an image on an electron-sensitive photographic plate (or a fluorescent screen) with the aid of electromagnetic lenses.

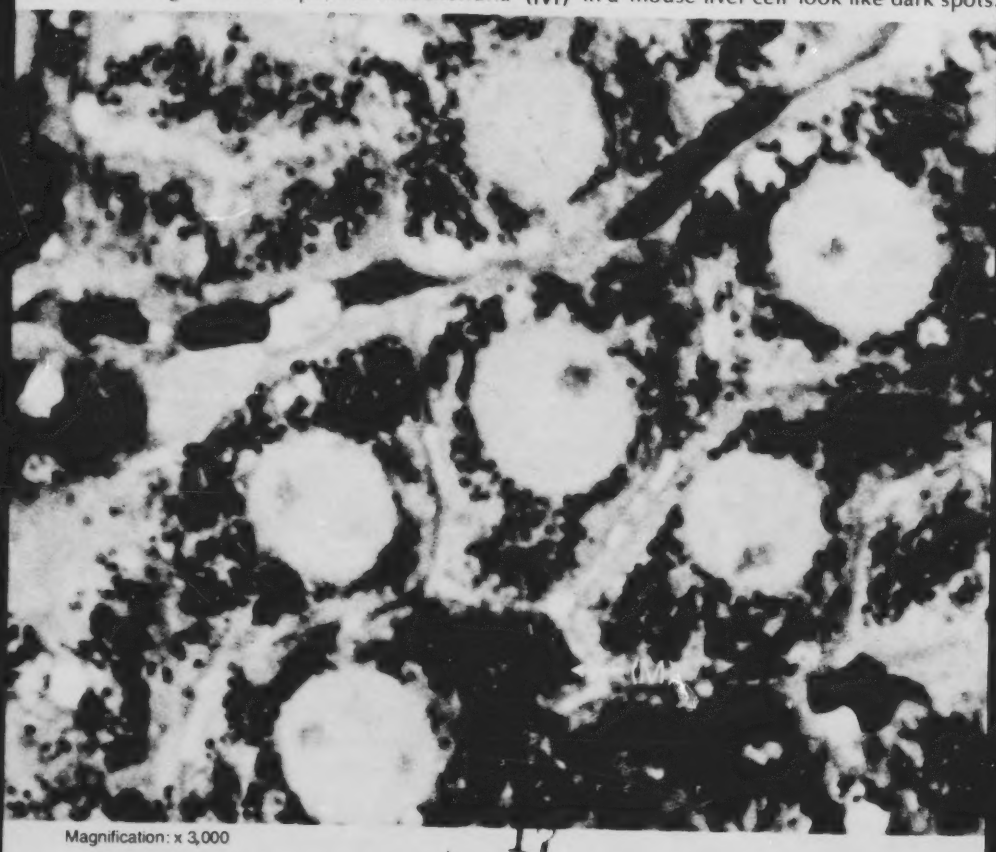
If pushed to the limit, electron microscopes could theoretically resolve objects as small as .025 angstroms, half the .05 angstrom wavelength, which is smaller than the diameter of an atom. Actually, however, the best instrument available today can "see" down to 2 or 3 angstroms—an incredible feat, for although this does not make atoms visible, it does allow researchers, for the first time, to distinguish individual molecules of biological importance. In effect, it can magnify objects up to 1 million times. Nevertheless, all electron microscopes suffer from a serious drawback: Since no specimen could survive under their high vacuum, they cannot show the ever-changing movements and reactions that characterize a living cell.

The first electron microscopes were used to study crystals and were impractical for the study of cell structure. It took years to modify and improve them. Simultaneously, researchers had to learn how to cut thinner and thinner slices of cells, sometimes down to a thickness of only a few hundred angstroms, so that electrons



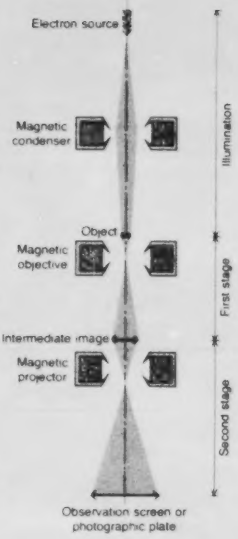
LIGHT MICROSCOPE

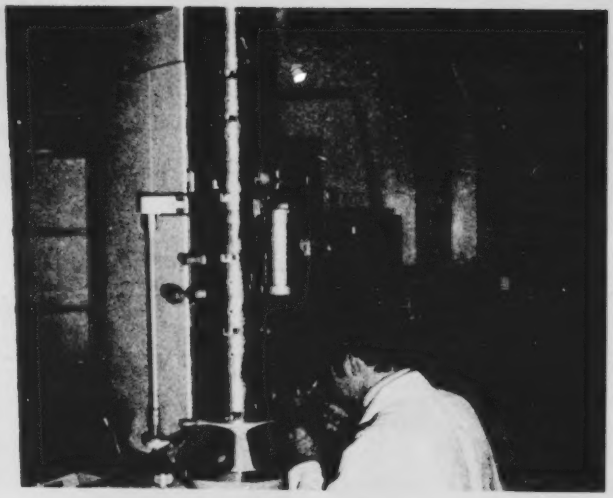
Under a light microscope, the mitochondria (M) in a mouse liver cell look like dark spots.



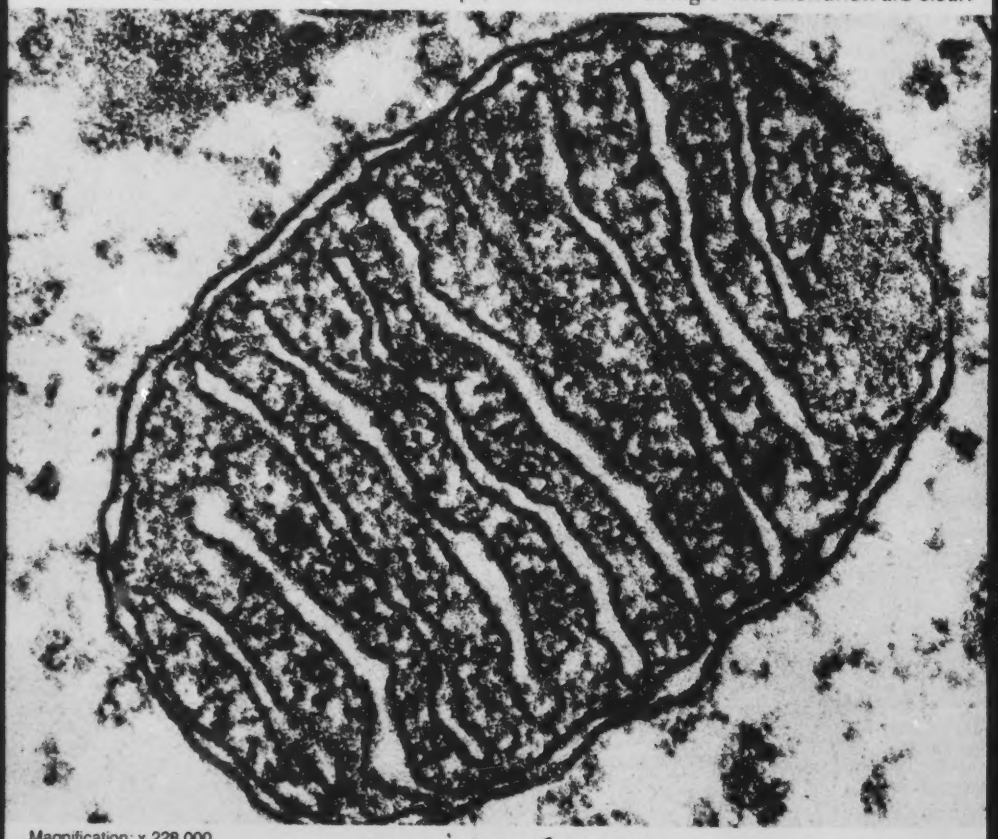
Magnification: x 3,000

ELECTRON MICROSCOPE





Under a high-powered electron microscope, the details of a single mitochondrion are clear.



Magnification: x 228,000

could pass through them. To ensure contrast between different parts of the otherwise transparent cell so as to reveal its structure, new staining techniques had to be devised, involving heavy metals; these are very dense to electrons, and different parts of the cell take them up to a different extent. The cell sections also had to be "fixed" in new ways, to preserve them, and embedded in new kinds of materials (mostly transparent plastic). Altogether, it wasn't until the early 1950's that the electron microscope was ready to make its major contributions to the study of cells.

While the cytologists (biologists who study cells) peered through their microscopes at smaller and smaller fragments of cells, in an attempt to understand their structure, another group of scientists was pursuing an entirely different, but equally important, line of research.

This line goes back to Antoine Lavoisier, the 18th-century French scientist who explained the role of oxygen in the respiration of both plants and animals, established the composition of water and other compounds, introduced quantitative methods in the study of chemical reactions, and thereby founded modern chemistry. In the 19th century, chemists isolated and identified many of the constituents of living cells—for example, hemoglobin, the red pigment of blood, and chlorophyll, the green pigment in plants. They discovered that compounds taken from animal tissue consisted of the same chemical elements as non-living materials. They isolated the nucleic acids, which are now known to govern heredity and protein synthesis. They began to study proteins, essential chemical components of living cells, and especially those proteins which control the chemical reactions that maintain life, the enzymes.

When dealing with cells, biochemists behave quite unlike the microscopists, who have enormous respect for the details of the cell's structure. The biochemists simply grind up large quantities of cells to release their contents into a solution (this is called "homogenizing" them) and then analyze the mixture (called the homogenate). This

means, first, separating the mixture into some of its component parts. Usually this is done with a centrifuge, a machine that separates particles according to their size and density by whirling them around at varying speeds. The heaviest and largest particles are thrown to the bottom of the test tube most rapidly, followed by somewhat lighter and smaller components, until at the highest speed there remain only the smallest and lightest particles at the top.

In 1925 a Swede, Theodor Svedberg, developed an instrument which would prove at least as revolutionary as the electron microscope: the ultracentrifuge, a machine that spun its samples at such high speeds and with such force (it could attain hundreds of thousands of times the force of gravity) that many of the smaller and lighter components of the cell and even proteins and nucleic acids could be collected separately and studied for the first time.

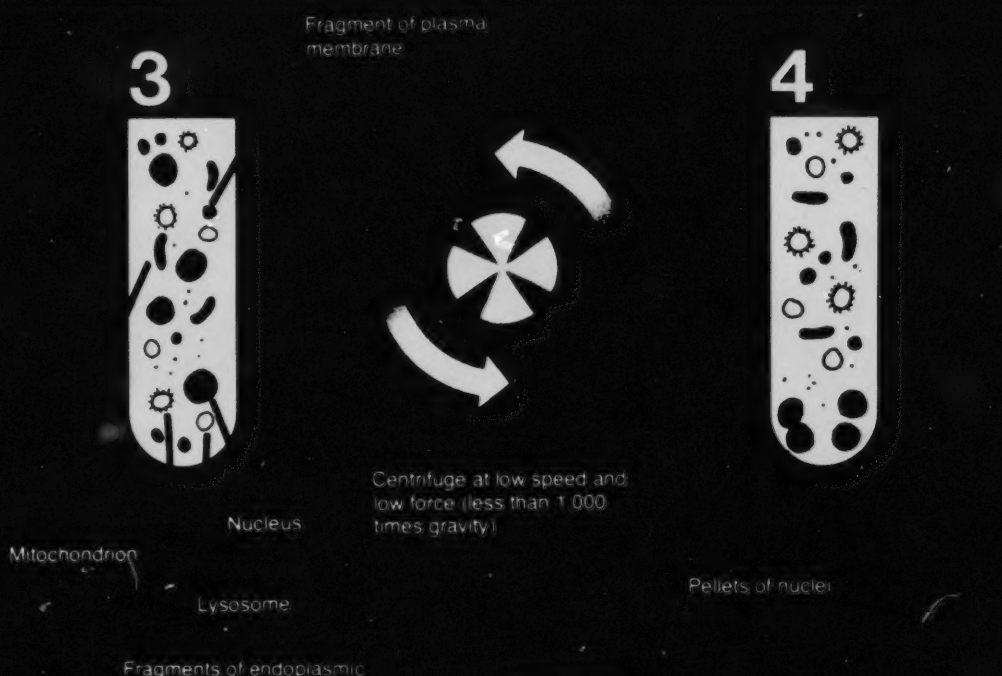
The significance of this new technology did not become apparent until years later. For a long time the biochemists seemed interested only in the chemical reactions of the cell as a whole—for example, what allowed it to obtain energy or to synthesize proteins. The men who worked with ultracentrifuges gave little thought to what the various fragments they dealt with represented in the cell—what they looked like, how they were organized, or how they related to one another. Very often the biochemists gave these fragments names of their own, unaware of the fact that another group of scientists had already examined and named them.

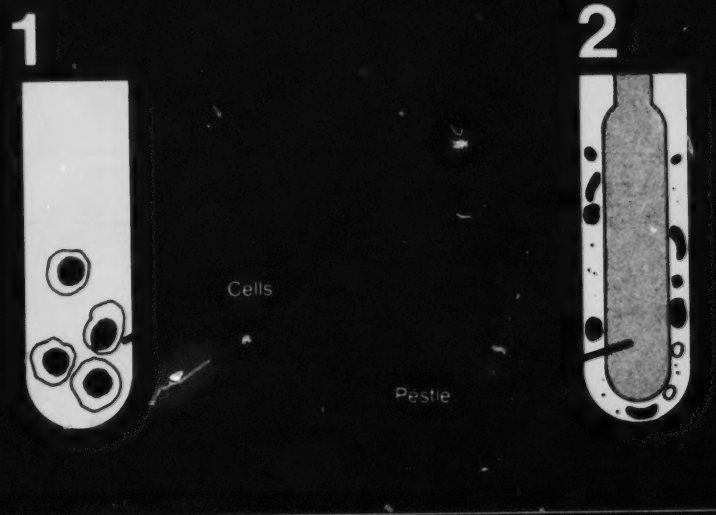
"There were two classes of people, and they didn't communicate with each other at all!" recalls Dr. DeWitt Stetten, Jr., Deputy Director of the NIH. The biochemists went on separating things with their centrifuges and making surprising discoveries that they didn't know how to interpret. The electron microscopists went on finding smaller and smaller particles in the cell and wondering what they did.

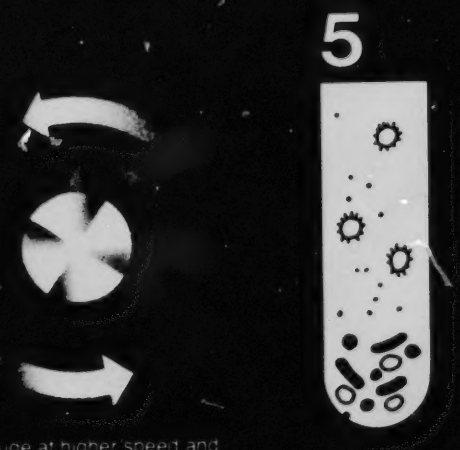
Finally, in the 1950's, the two groups began to edge

HOW BIOCHEMISTS BREAK UP CELLS AND ISOLATE THEIR COMPONENTS

To study the particles in cells biochemists begin by breaking up the cells with a pestle and releasing their contents in a solution. The mixture or homogenate is then whirled around in a centrifuge at various speeds to separate the particles according to their size and density. The heaviest organelles settle to the bottom first. The remaining cell fragments are then transferred to a new tube and centrifuged at higher speed. The process can be repeated again and again to isolate progressively smaller particles.





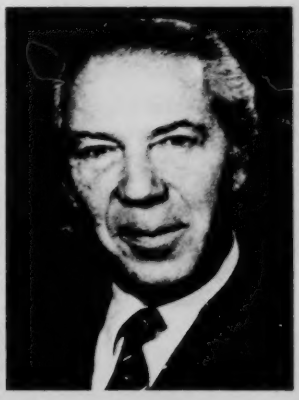


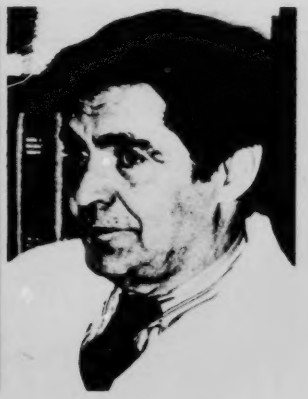
Centrifuge at highest speed and greatest force (100,000 times gravity) to separate fragments of endoplasmic reticulum and ribosomes

Pellets of mitochondria and lysosomes

closer together. "It was an important fusion," says Stetten. By that time electron microscopes had become extremely powerful. When the microscopists discovered that the biochemists' pieces matched what they had been seeing under their microscopes, and the biochemists discovered that the microscopists could actually *see* what they had been analyzing, there was great rejoicing and euphoria on both sides.

It was, in a way, like coming out of the Dark Ages.





Three of the 29 scientists who have won the Nobel Prize for their discoveries in cellular and molecular biology since 1953, Albert Claude of the Institut Jules Bordet in Brussels, Belgium, Christian de Duve of Rockefeller University in New York and Louvain University, Belgium, and George Palade of Yale University shared the Prize in 1974 for their work on the structure and function of the cell. They are representative of thousands of researchers who have made important contributions to modern cell biology throughout the world.

THE BIRTH OF MODERN CELL BIOLOGY

When a Belgian physician, Andreas Vesalius, published the first detailed descriptions and drawings of the organs of the body in 1543, he started a Renaissance in medical science. Strictly forbidden in medieval times, the dissection of human cadavers had not been practiced by Western physicians for over a thousand years, until the 14th century. Vesalius' precise descriptions of human organs suddenly raised important questions about their functions, and in attempting to answer these questions, anatomy became a scientific discipline.

Another Renaissance in medical science began roughly 30 years ago, when the electron microscope revealed that each cell has various organs of its own. These organs, or organelles, are as essential to the life of the cell as the heart, liver and brain are essential to the life of the human body. And once again, the awareness of so many different structures, each with a characteristic size, shape, and function, is raising questions which challenge older concepts of health and disease.

The early 1950's saw an avalanche of discoveries about the world within the cells of animals and plants. A whole new vocabulary had to be developed for such unfamiliar structures as lysosomes, mitochondria, ribosomes, the rough endoplasmic reticulum, the smooth endoplasmic reticulum, microfilaments, microtubules, the plasma membrane, and others. At first these sounded exotic and rather forbidding, but by now each organelle has emerged with a personality of its own, and scientists speak of them not only with assurance but even, at times, with affection or humor. "I regret somewhat that I cannot

Despite their extraordinary variety, the cells of all species are made of the same fundamental materials: nucleic acids, proteins, lipids, carbohydrates, water and salt.

be in closer touch with my mitochondria," writes Lewis Thomas, president of the Memorial Sloan-Kettering Cancer Center in New York, in his book, *The Lives of a Cell*. "If I concentrate, I can imagine that I feel them; they do not quite squirm, but there is, from time to time, a kind of tingle."

In their rush to study the new particles' anatomical organization, chemical functions and molecular structure, scientists have had to merge many disparate skills. Alone, each group of specialists could uncover only a small piece of the jigsaw puzzle, but by combining their techniques they have been able to delve further and further

into the mysteries of the cell.

For example, they have begun to decipher the composition and three-dimensional structure of enzymes and other essential proteins. Enzymes are extraordinarily efficient catalysts which can speed up chemical reactions up to 100,000 times. They do this at body temperature and in a neutral solution, when chemists would have to use very high temperatures and potent chemicals, such as strong acids or bases, to achieve the same speed. We depend on enzymes to break down the food we eat and provide us with energy; to get rid of unwanted chemicals in our cells; to synthesize other proteins, nucleic acids, fats and carbohydrates; to maintain the chemical balance within our cells; and to perform hundreds of other vital functions. While the biochemistry of cells is extremely complex, each basic step consists of a single chemical reaction, catalyzed by a specific enzyme. A single bacterium may have several thousand different enzymes, and a mammal many more. Yet each of these enzyme molecules is so intricate that two decades ago it seemed beyond the powers of chemistry and physics to understand its structure. Although the structures of only a small number of enzymes have been uncovered to date, this achievement—which depended on X-ray crystallography and other new methods—has been one of the triumphs of molecular biology. It is changing our view of key operations within the cell, such as the energy transformations within the mitochondrion.

The joint effort of electron microscopists, biochemists, physical chemists, X-ray crystallographers, physiologists and geneticists, brought to bear on such problems, has produced modern cell biology.

GENERAL CHARACTERISTICS OF THE CELL

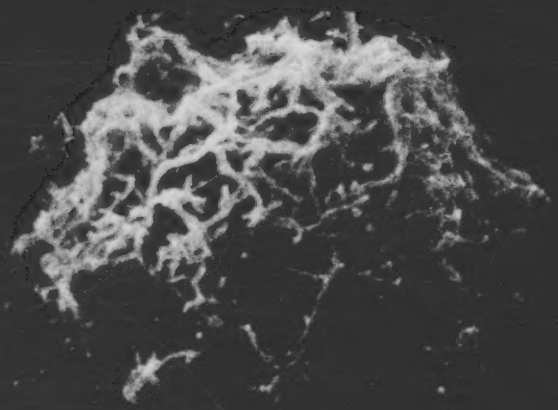
Each of us starts life as a single cell, a microscopic package which contains directions for everything that we can become.

This cell is defined and separated from the rest of the world by a membrane, a transparent film so thin that it could not be seen under any light microscope. For years scientists debated whether such a membrane truly existed—perhaps it was just an illusion? Despite its ethereal appearance, however, the surface membrane is not only real but exceedingly powerful, controlling everything that goes in and out of the cell and relaying vital messages. Similar membranes enclose or make up a large number of the cell's organelles.

"It takes a membrane to make sense out of disorder in biology," writes Lewis Thomas. "You have to be able to catch energy and hold it, storing precisely the needed amount and releasing it in measured shares. A cell does this, and so do the organelles inside it. . . .you can only transact this business with membranes in our kind of world."

Sheltered by the cell's surface membrane (which is also called the plasma membrane), different configurations of organelles move about in a watery environment. The number and kinds of organelles in each cell depend on its function.

Now that researchers have become acquainted with these organelles, they can often guess at a cell's specialty from its structure: A cell that contains many mitochondria, for instance, *must* be involved in producing large quantities of energy. (It was once calculated that



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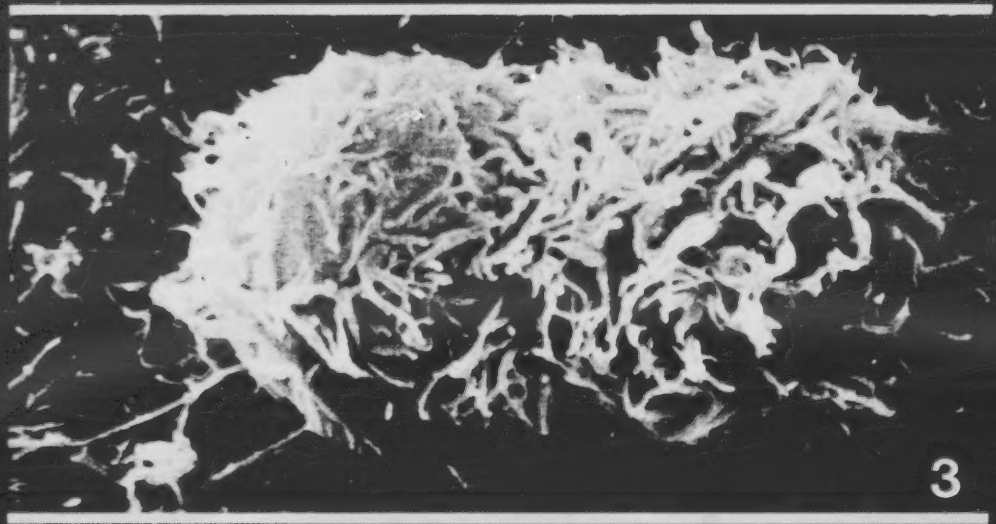

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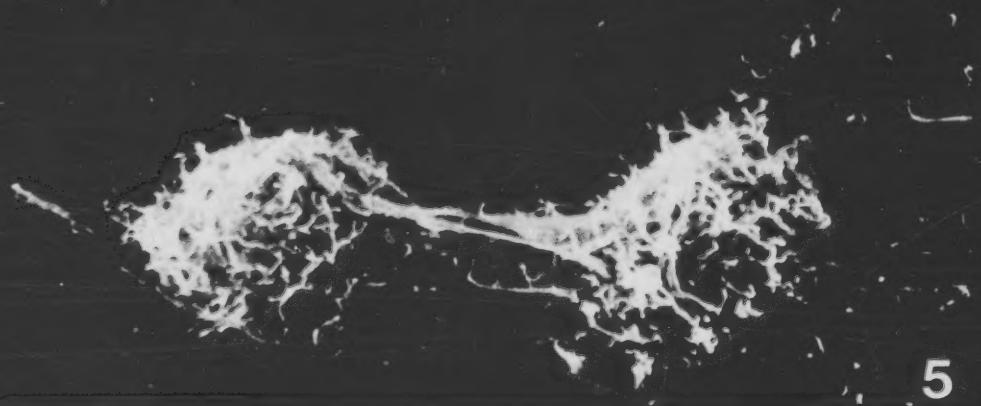

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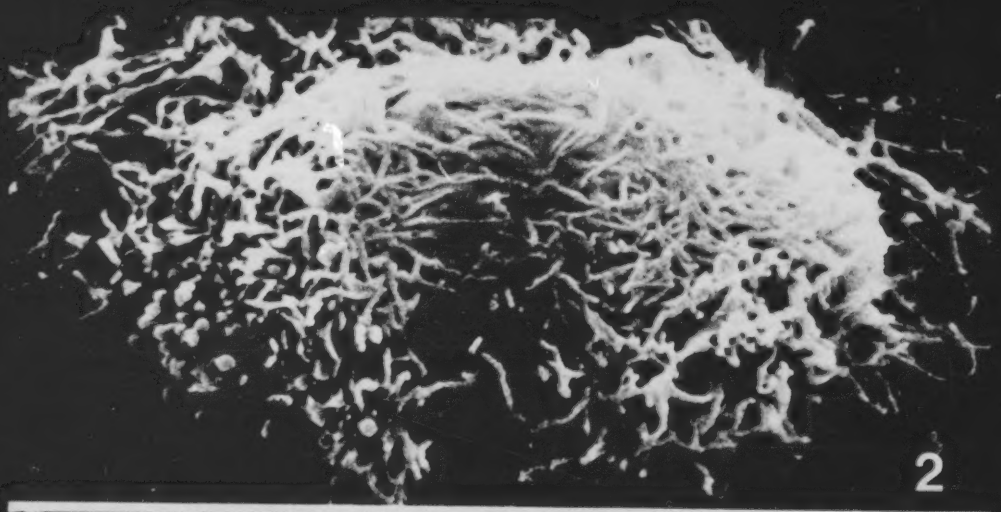
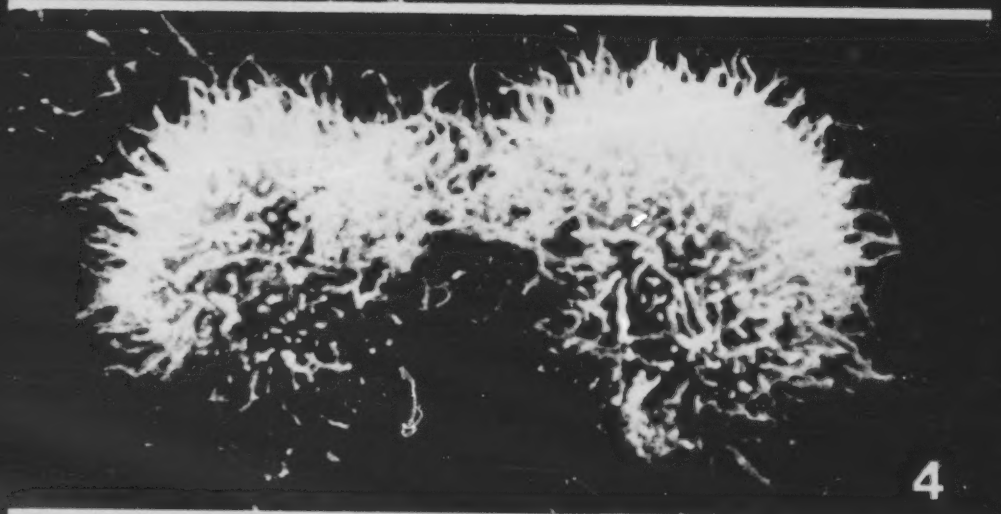
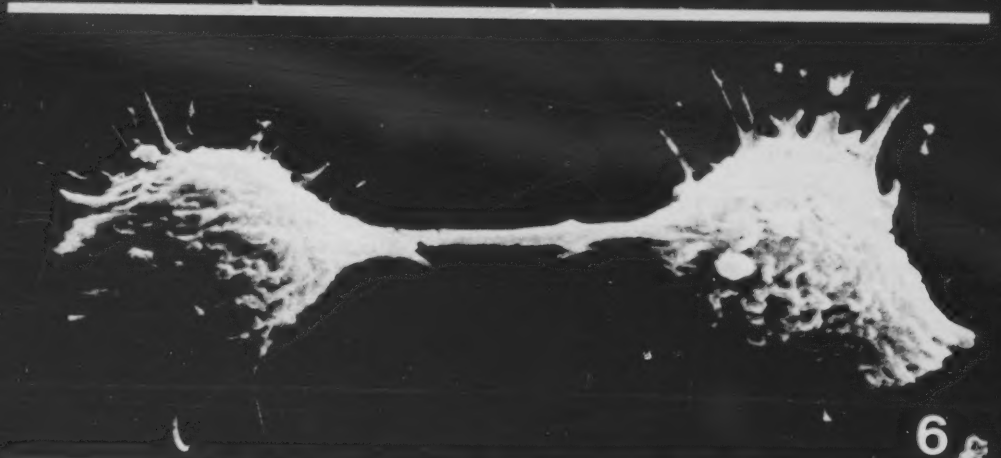
A human cell splits: These SEM (scanning electron microscope) photographs show one cell dividing into two identical daughter cells. The cleavage furrow between the daughter







cells deepens as the cells move apart. The hair-like projections on the cell surface are microvilli, cytoplasmic extensions which seem to be involved in cell motion.

bumble-bees cannot fly, since there seemed no way for their short wings to get enough lift—yet obviously they do fly, despite their weight, and one reason is that the cells in their wing muscles contain exceptionally large numbers of mitochondria which supply them with the energy to beat at enormous speed). A cell in which ribosomes are prominent must be synthesizing proteins. A cell with a great many lysosomes must be destroying wastes. And so on.

The single cell with which we start life divides again and again. As Daniel Mazia, Professor of Zoology at the University of California, puts it, the story of the cell cycle is "Double or nothing. With few exceptions, a living cell either reproduces or dies; the principle is so simple that no one has bothered to call it a principle. A cell is born in the division of a parent cell. It then doubles in every respect: in every part, in every kind of molecule, even in the amount of water it contains."

The process is particularly clear in single-celled organisms such as amoebae, which may live forever through doublings. Each cell annihilates its individual existence in the production of two daughter cells, which repeat the process roughly 40 hours later, until limited by the food supply, eaten by another organism, or destroyed in other ways. Some bacteria reproduce every 20 minutes.

In more complex organisms, however, the life span of individual cells varies. "The governance of an organism such as a higher animal, which is a society of cells, dictates that some of the cells in the society will reproduce and that others will not," writes Mazia. "In general, the cells of tissues that perform special services for the entire organism, such as cells of the nervous system and the muscular system, do not reproduce at all." We are born with our full complement of brain neurons. Most of these neurons live as long as we do, but when one dies it is not replaced.

By contrast, the white phagocytic (scavenger) cells in our blood are replaced every two or three weeks. The life span of our red blood cells is three to four months. Our

skin cells, too, keep being replaced. In such tissues, "The rate of production of new cells is nicely modulated to compensate for the continual loss of old cells," Mazia points out. In case of wounds or infections, when many cells are lost, the remaining cells multiply rapidly until the number of new cells is sufficient to replace what was lost, and then stop. It is only in cancer that the cells repeat the cycle without restraint.

Surprisingly, *all* cells, whether of plant, bacteria, mouse or man, are made of the same fundamental materials: nucleic acids, proteins, lipids, carbohydrates, water and salts.

"The uniformity of the earth's life, more astonishing than its diversity, is accountable by the high probability that we derived, originally, from a single cell," notes Lewis Thomas. "It is from the progeny of this parent cell that we take our looks; we still share genes around, and the resemblance of the enzymes of grasses to those of whales is a family resemblance."

The genetic material in all these cells is DNA (deoxyribonucleic acid), a large molecule which directs the making of duplicate cells according to a complex code. DNA also directs the building of proteins within the cell. Even the smallest and simplest living cells—the mycoplasma—contain a relatively large amount of DNA, enough to code for up to a thousand different proteins. Every human cell has about 6 feet of DNA strands, and every adult carries about 100 billion miles of ultra-thin DNA strands in his body—a distance greater than the diameter of the solar system.

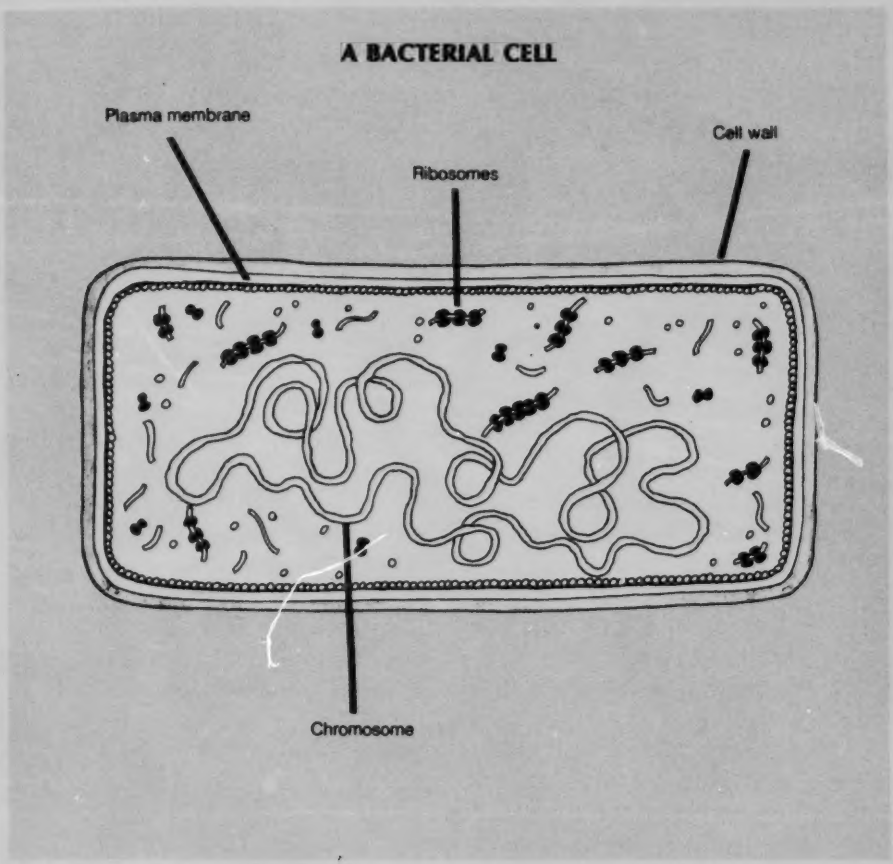
This DNA is concentrated in the cell's nuclear region. But there is a fundamental distinction between two major categories of cells:

The *procaryotic* cells, which include the bacteria, mycoplasma and blue-green algae, do not have any membrane around their nuclear region. In fact, they do not have any membrane-bound organelles at all.

The *eucaryotic* ("proper nucleus") cells do have a double membrane to separate their nucleus from the

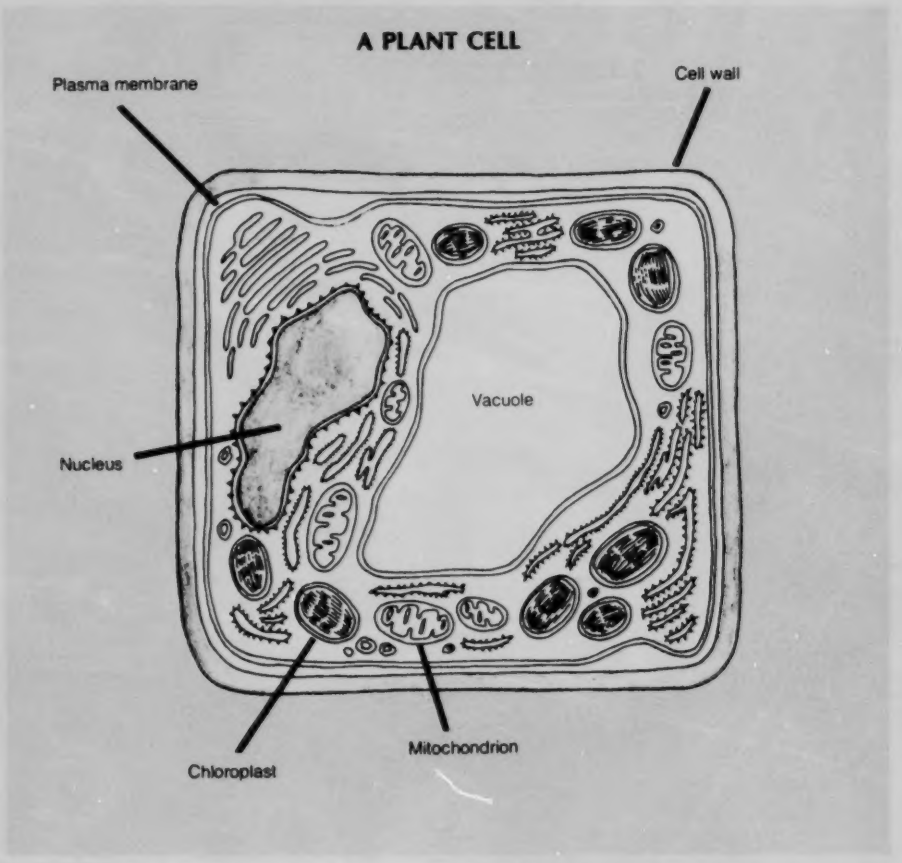
cytoplasm, as well as many other internal membranes to segregate their organelles. The cells of all animals and plants (except blue-green algae) and those of one-celled protozoa fall in this category.

Only the eucaryotic cells are able to combine with one another to form multicellular systems—an important step



Bacterial cells have no nucleus; their chromosomes, smaller and simpler than those of animal cells, are not enclosed in a membrane. As this diagram of an *Escherichia coli* bacterium shows, bacteria do not have any membrane-bound organelles at all. They cannot combine with one another to form multicellular systems, as plant or animal cells do.

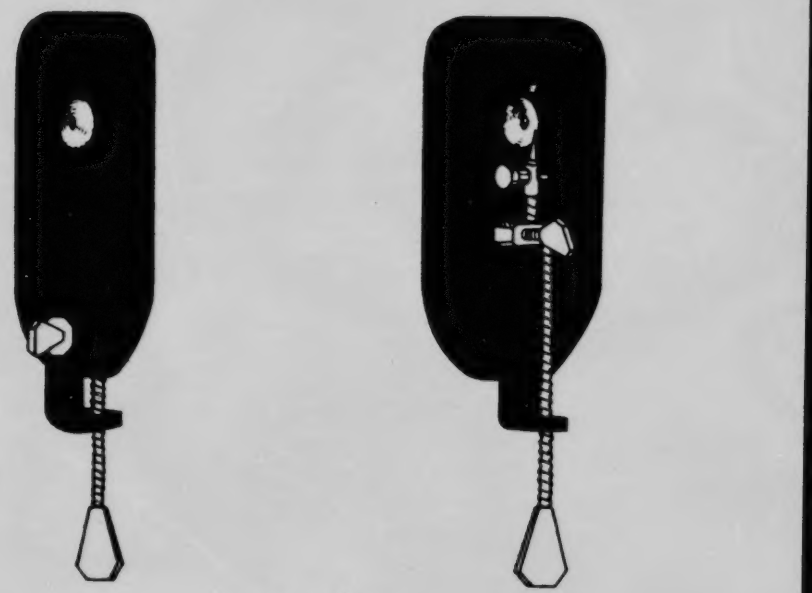
up the evolutionary ladder. And while, in general, the procaryotic cells produce only exact duplicates of themselves, the eucaryotic cells are capable of differentiation into many different kinds of cells, at least in higher organisms. This gives the eucaryotic cells certain obvious advantages. However, the procaryotes have advantages of



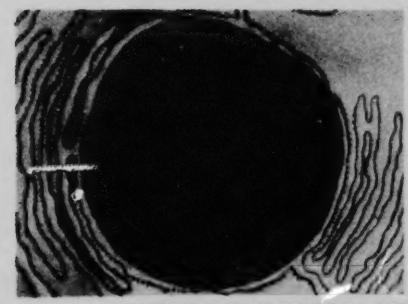
One thousand times larger than bacterial cells, plant cells have a well-defined nucleus, as well as many membrane-bound organelles. They also have chloroplasts which allow them to utilize solar energy in photosynthesis. A rigid cell wall made of cellulose lies outside their plasma membrane. The large vacuole, containing water and salt, preserves osmotic pressure.

their own: simpler nutritional requirements, and much more rapid growth and division. They are not necessarily inferior. As Mazia puts it, the differences between the two types of cells are simply "different ways of making a living."

Some of the most important discoveries in modern cell biology have involved the eucaryotic cell and its organelles, beginning with the most prominent organelle of all, the nucleus.



This is the actual size of a typical microscope built by Leeuwenhoek. He peered through the tiny lens opening on one side of a metal plate (left) to see the specimen mounted on the point of a pin on the other side (right). The specimen could be moved into focus by a system of screws.



THE NUCLEUS—THE CELL'S COMMAND CENTER

The nucleus is the biggest, densest, most obvious structure in the cell—the first to be recognized by the microscopists, and the first to be isolated in the biochemists' centrifuge.

Ironically, it was not a scientist but a cloth merchant, Anton van Leeuwenhoek, who saw the nucleus of a cell for the first time. Leeuwenhoek, who lived in Delft, Holland, ground his own lenses as a hobby—once he made a lens out of a grain of sand. His hobby became a passion as he examined everything from pond water to the scum on his teeth. Unfortunately, he jealously guarded his methods, and after he died it took more than a century for others to make equally good instruments. Even then they did not have his remarkable eyesight: He managed to perceive things through his single lens that modern cytologists need a compound microscope to see.

In 1702, while examining the blood cells of a fish, Leeuwenhoek discovered "a little clear sort of light in the middle," he reported in a letter to the Royal Society in London.

This was the first inkling anyone had that animal cells were not just cavities, but had an internal structure. A century later, the nucleus of a plant cell was seen for the first time (by the Scottish botanist Robert Brown, in 1828) and in 1830 Johann Evangelista Purkinje, a Bohemian physiologist, described the relatively enormous nucleus of a hen's egg.

However, nobody knew what this nucleus did. Several researchers noted that before a cell divided, the nucleus divided. Yet it wasn't until the beginning of the 20th cen-

tury that they grasped the connection between the rod-like chromosomes which had been observed in the nucleus and the transmission of hereditary traits. At that point, the importance of the nucleus became clear.

The nucleus is the cell's command center. It contains the genes, the units of hereditary material (DNA) which give directions for everything the cell is and will be, and thus controls the cell's reproduction and heredity. Yet it also responds to the environment. Only certain genes are "turned on" to give orders for the production of specific proteins at any particular time. The molecules which switch these genes on or off come from the cytoplasm, where they are generated as a result of interaction between the surface membrane and the environment. Thus the commands from the nucleus are always influenced by what goes on outside the cell. While the genes contain the total range of the cell's possibilities, the environment selects which of these possibilities for growth and development will be expressed.

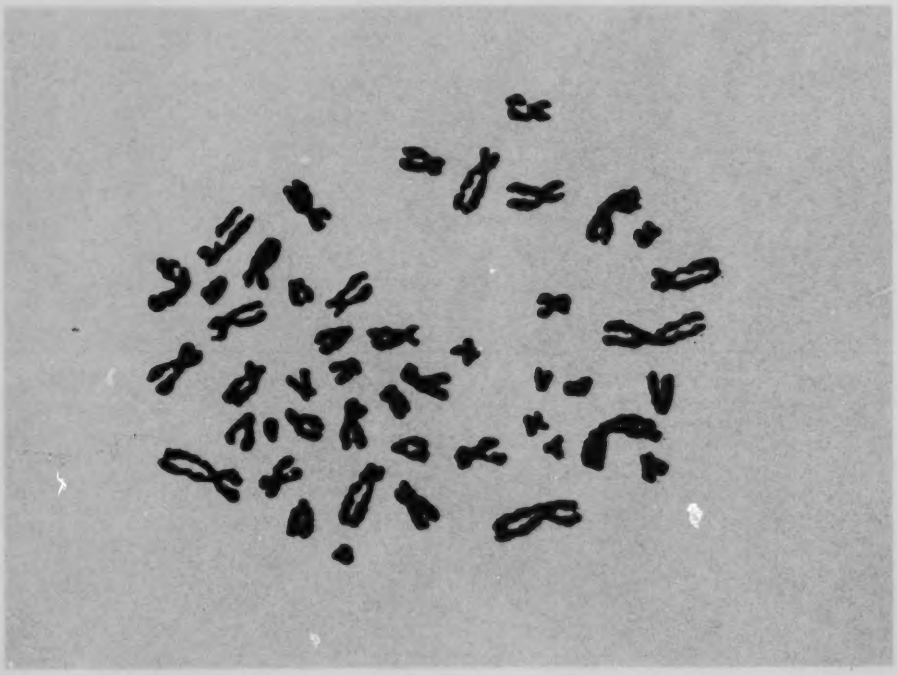
Without a nucleus, cells die rapidly, excepting only the mammalian red blood cells—the only common animal cells to be deprived of nuclei—which do live a few months. Of course these cells have no progeny. (The mammalian red blood cells are formed in the bone marrow through a peculiar process in which half of the newly-made cells differentiate to become red blood cells, while the other half remain in the bone marrow, to produce a new crop of cells). Actually the mammalian red blood cells are just bags for hemoglobin, which carries oxygen through the body. Other cells whose nuclei have been removed surgically, or destroyed, survive only a few hours.

As might be expected, the nucleus is constantly active. Before cell reproduction, new DNA must be synthesized and every single gene must be replicated. These genes, which are linked together into chromosomes, are then separated into two duplicate sets. At this point the nuclear envelope breaks down, the two sets of chromosomes move to opposite poles of the cell, and the

cell divides, forming two identical daughter cells.

Meanwhile the nucleus goes through extraordinary changes in shape, from spherical to oval and to a strange assortment of folds or twists, until it actually disappears—to be re-formed, in duplicate, at the end of cell division.

In addition to all this reproductive activity, the genes in the nucleus selectively direct the synthesis of thousands of enzymes and other proteins in the cytoplasm. This is done through the "transcription" of information from various parts of the DNA molecules into new strands of nucleic acid (messenger-RNA) which carry it into the cytoplasm.



With this historic photo, Drs. Joe Hin Tjio and Albert Levan showed that there are 46 individual chromosomes in a normal human cell. Half of these chromosomes come from the mother, half from the father, and they are usually counted in pairs, except for the sex chromosomes (X and Y chromosomes). Magnification: x 2,300.

As long as the genes are busy replicating themselves or transcribing their information, the chromosomes into which they are linked cannot be distinguished—they look like a jumble of threads. It is only during mitosis that these incredibly thin strands of DNA and protein become thick enough to be seen as rods under the light microscope. During this process the DNA strands condense through interaction with various proteins, coil themselves again and again, and pack themselves into highly complex, tight bundles that are about 8,000 times shorter than the original strands.

It took years of effort and many technological advances before the chromosomes of all kinds of cells could be seen clearly enough to be counted accurately. Each species of plant or animal has a characteristic number of them, and these chromosomes also vary in size, length and other properties. It was a major achievement when the number of chromosomes in human cells—46—was finally established in 1956 by Joe Hin Tjio of the NIH and Albert Levan of Sweden, who also succeeded in identifying each individual human chromosome by its characteristic shape.

The cells which will form a new human being—the egg cells and sperm cells—depart from this norm of 46 chromosomes per cell; each carries only half the usual complement. Thus, when a human egg and sperm fuse normally, the new cell again has a total of 46 chromosomes, or 23 pairs, with one chromosome in each pair coming from the mother and one from the father.

Several forms of mental retardation and dozens of other disorders have now been traced to gross errors in the number or shapes of the chromosomes in each cell. In recent years it has become possible to test for several of these prenatally, through a technique called amniocentesis. For example, Down's syndrome (mongolism) can now be detected before birth, by withdrawing a sample of amniotic fluid from the expectant mother's uterus with a hypodermic needle and counting the chromosomes in cells which the growing fetus shed in this fluid. (Down's

syndrome is caused by an extra chromosome, believed to result from the incomplete separation of the chromosomes during the formation of the egg; this occurs most frequently when the mother is over 40 years old). Thousands of parents have taken advantage of this forecasting ability early in pregnancy.

The nuclei of individual cells are visible with a good light microscope at a magnification of only 100. At a magnification of 2,300, Tjio and Levan succeeded in examining individual chromosomes. But going one step further and investigating the genes, the units of heredity inside the chromosomes, proved far more difficult.

This is where the chemists and later the molecular biologists made some of their most important contributions. As early as 1869, a Swiss chemist, Fredrick Miescher, isolated some nuclear material from the pus cells on discarded hospital bandages and analyzed its content: phosphorus, carbon, oxygen, hydrogen and nitrogen. The material was later called nucleic acid and shown to consist of two kinds of substances, one containing the sugar ribose (this was ribonucleic acid, or RNA) and the other containing deoxyribose (this was deoxyribonucleic acid, or DNA). The substance in the chromosomes was identified as DNA. In 1944, Oswald Avery and his associates at the Rockefeller Institute discovered that DNA was directly involved in transferring hereditary characteristics from one strain of bacteria to another. And then everything speeded up.

By 1951, Maurice Wilkins and Rosalind Franklin at King's College, London, were studying the X-ray diffraction patterns of purified fibers of DNA—patterns which proved crucial in understanding the structure of DNA. Two years later, in 1953, Francis Crick and James Watson, working at the Medical Research Council laboratories in Cambridge, England, proposed their famous *double helix* model of the DNA molecule, which explained how DNA is built and how it replicates. Watson, Crick and Wilkins later won the Nobel Prize for this achievement.

From then on, genes—the units of heredity whose exis-

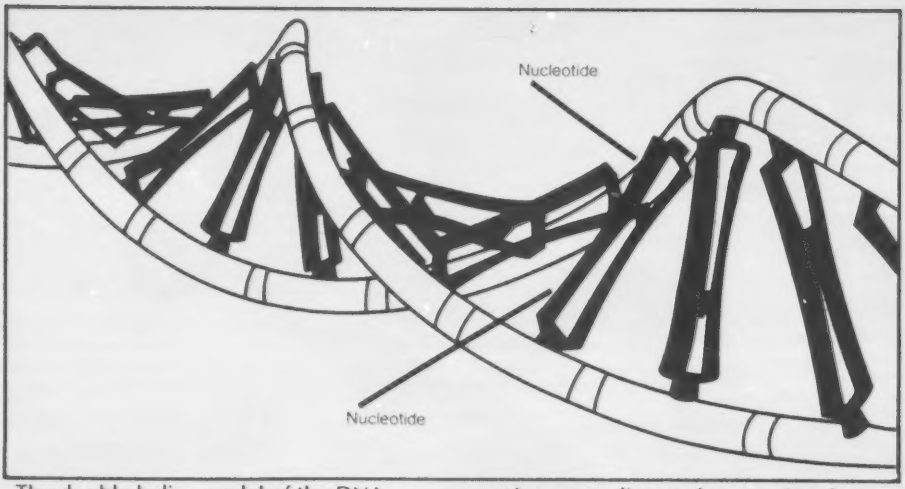
tence was only hypothesized by earlier scientists—could be studied and analyzed in terms of their biochemical composition. According to Watson and Crick, the DNA molecule consists of different sequences of nucleotides (DNA building blocks linked together in helical or spiral form, like an almost endless, twisted rope ladder). A single gene might be a section of this rope ladder perhaps 2,000 steps long. And every step, or rung, in the ladder is made up of two nucleotides which fit together according to their bases. (Nucleotides consist of one of four chemical bases—adenine, thymine, guanine and cytosine—attached to a chain of sugar-phosphates which acts as an outer backbone. An adenine base (A) will fit only with thymine (T), and a guanine base (G) will fit only with cytosine (C), so that the sequence of bases on one half of the rung (for example, AGCG) determines the sequence on the other half (TCGC). This is the alphabet of the nucleic acids—a small set of "letters" with which, as with the ABC's, an infinite number of messages and instructions can be written.

In the early 1960's, the language in which such instructions were written—the genetic code—was deciphered by Marshall Nirenberg of NIH, Severo Ochoa of New York University and Har Gobind Khorana of the University of Wisconsin, for which they, too, won the Nobel Prize. The code consists of triplets of nucleotides which are "read" in sequence along the DNA molecule. Each triplet corresponds to one word, i.e., one of the 20 amino acids, which are the building blocks of protein. This is the universal "language of life."

Each gene is a series of triplets which gives the instructions for building a specific protein and thus influences a specific trait, such as blue eyes.

In 1976, after nine years of work, Khorana produced an artificial gene out of laboratory chemicals and showed that it functioned normally when he inserted it in a live bacterium.

Meanwhile, a new technique using "recombinant DNA" was developed for studying individual genes: After



The double helix: model of the DNA (deoxyribonucleic acid) molecule which embodies the code of heredity, as conceived by Francis Crick and James Watson in 1953. All living things reproduce themselves according to the genetic information in different sequences of DNA subunits (nucleotides). Genes, the units of heredity, consist of nucleotides linked together in a helical or spiral form.

UUU	Phe	UCU	Ser	UAU	Tyr	UGU	Cys
UUC	Phe	UCC	Ser	UAC	Tyr	UGC	Cys
UUA	Leu	UCA	Ser	UAA	stop	UGA	stop
UUG	Leu	UCG	Ser	UAG	stop	UGG	Trp
CUU	Leu	CCU	Pro	CAU	His	CGU	Arg
CUC	Leu	CCC	Pro	CAC	His	CGC	Arg
CUA	Leu	CCA	Pro	CAA	Gln	CGA	Arg
CUG	Leu	CCG	Pro	CAG	Gln	CGG	Arg
AUU	Ile	ACU	Thr	AAU	Asn	AGU	Ser
AUC	Ile	ACC	Thr	AAC	Asn	AGC	Ser
AUA	Ile	ACA	Thr	AAA	Lys	AGA	Arg
AUG	Met	ACG	Thr	AAG	Lys	AGG	Arg
GUU	Val	GCU	Ala	GAU	Asp	GGU	Gly
GUC	Val	GCC	Ala	GAC	Asp	GGC	Gly
GUA	Val	GCA	Ala	GAA	Glu	GGA	Gly
GUG	Val	GCG	Ala	GAG	Glu	GGG	Gly

U – uracil (thymine)
C – cytosine
A – adenine
G – guanine
Ala – alanine
Arg – arginine
Asn – asparagine
Asp – aspartic acid
Cys – cysteine
Gln – glutamine
Glu – glutamic acid
Gly – glycine
His – histidine
Ile – isoleucine
Leu – leucine
Lys – lysine
Met – methionine
Phe – phenylalanine
Pro – proline
Ser – serine
Thr – threonine
Trp – tryptophan
Tyr – tyrosine
Val – valine

The genetic code: Each triplet of nucleotides codes for one amino acid, excepting three—the "stops"—which signify the end of a protein chain. Each gene is a series of triplets which gives the instructions for building a specific protein and thus influences a specific trait, such as blue eyes.

splitting some animal or human DNA into thousands of segments, scientists transfer one segment into a bacterium, where it is replicated and expressed together with the bacterium's own genetic material.

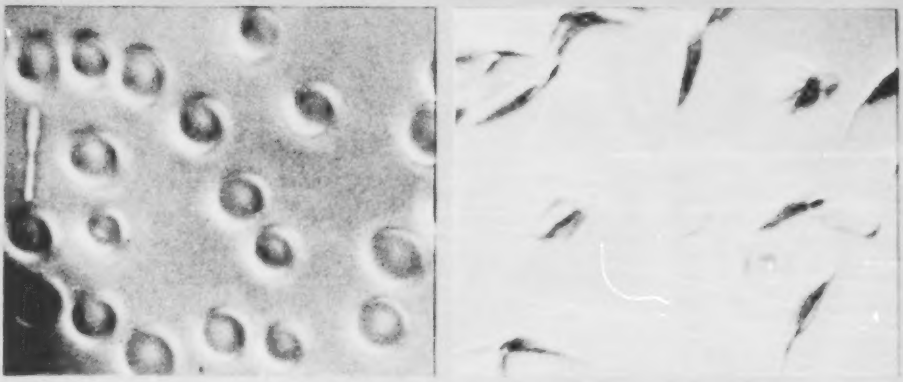
In many ways, then, scientists are developing the ability to manipulate genes. They are also learning to mitigate or prevent some of nature's genetic mistakes.

Genetic diseases used to be considered quite rare, but it is now recognized that innumerable persons suffer the consequences of disorders due wholly or in part to a defective gene or chromosome. Some 2,000 different genetic disorders have been identified.

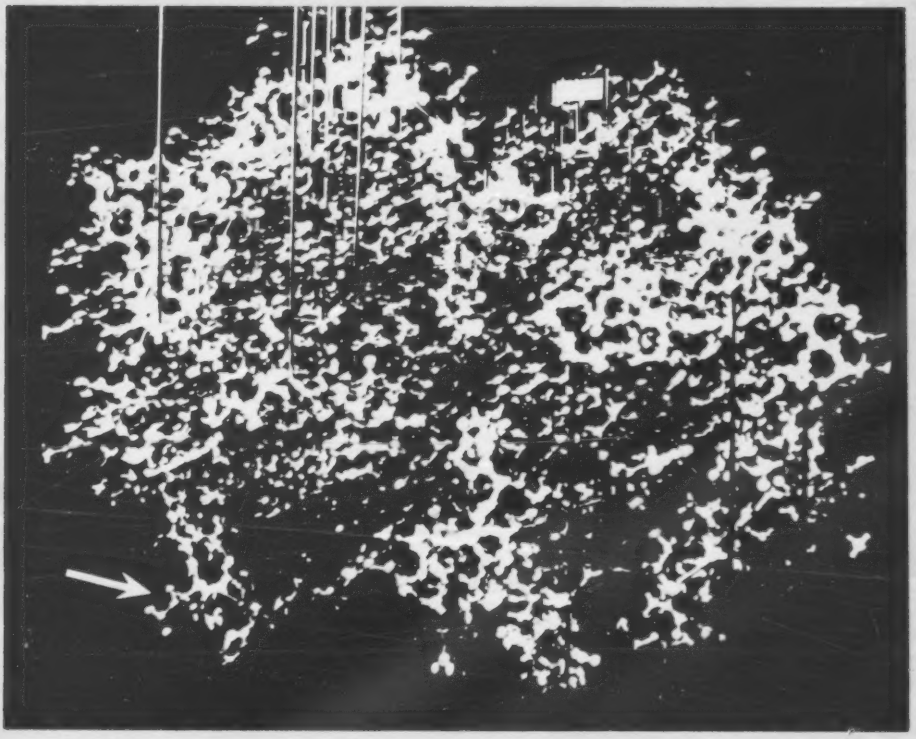
Sickle-cell disease, for example—a disease which affects some 50,000 Americans, mostly blacks, producing chronic anemia, jaundice, severe pain, poor resistance to infection and sometimes an early death—has been traced to a single gene and the resulting misplacement of just one amino acid out of 300 in the hemoglobin molecules of the victims' red blood cells. The cells then become distorted from their normal round shape, often into the shape of a crescent or sickle, and are altered in other ways as well. The abnormal cells may stick together, obstructing the small blood vessels and causing damage as well as pain, or be removed too rapidly by the spleen, causing anemia.

Over 2 million Americans are carriers of this defect. Although they may be perfectly healthy, if they marry one another they risk transmitting sickle-cell disease to their offspring: Each of their children will have a 25 per cent chance of inheriting the disease. A simple blood test can now identify people who carry the sickle-cell gene. Researchers are studying various techniques for detecting the defect prenatally, and several possible methods of treatment are under investigation.

While genetic defects cannot be corrected inside the cell—at least not with present techniques—increasing knowledge about their specific effects on human development has led to various forms of environmental treatment: medications, diet, or a change in life habits. In



In sickle-cell disease, many red blood cells are distorted from their normal disc shape, often into the shape of a crescent or sickle. These distorted cells may stick together, obstructing the smaller blood vessels, or break down too rapidly, causing anemia.



The faulty placement of only one amino acid out of 300 in this hemoglobin molecule changes its complex structure sufficiently to cause sickle-cell disease. (see arrow)

Wilson's disease, for instance, a dangerous accumulation of copper in the body can be treated by washing out this excess copper with other chemicals. The brain damage and mental retardation associated with another hereditary condition, PKU (phenylketonuria) can be reduced or prevented if a diet low in the amino acid phenylalanine is started immediately after birth. And if people who have an inherited deficiency of the enzyme G6PD (glucose-6-phosphate dehydrogenase) stay away from certain common substances—aspirin, vitamin K, certain antimalarial drugs, and even moth balls—they can avoid the risk of severe anemia.

Eventually, perhaps, it may become possible to turn on specific genes in the cell at specific times. Although every cell in the body has the same set of genes and all of these genes must be replicated before cell division, only certain genes are turned on to produce specific proteins at any given time. In specialized cells such as liver cells or bone cells, many genes are turned off permanently. But sometimes there are problems. In sickle-cell disease, for instance, the gene which makes normal hemoglobin in the fetus gets turned off after birth—as it should—but the newly activated, adult gene is defective. As scientists learn more about the switching-on and switching-off mechanisms, they may be able to avert the switch-off in such cases, or else re-activate the embryonic gene, which might lead to a treatment for the disease. Looking even farther into the future, researchers may yet learn to insert missing genes right into human cells to correct certain genetic mistakes.

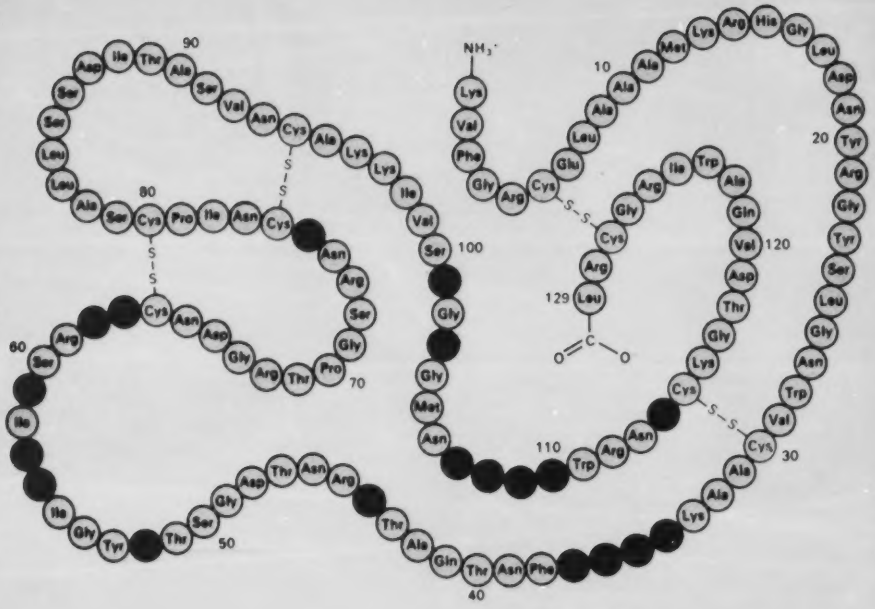
RIBOSOMES, OUR PROTEIN FACTORIES

Whenever the cell needs a protein, the cytoplasm alerts the nucleus with an as-yet-unidentified chemical message. The DNA of the appropriate gene or genes in the nucleus then issues the specific instructions for making this protein.

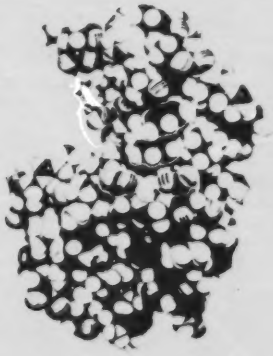
These instructions are transmitted not by the DNA itself, but by a close copy made out of a different nucleic acid, RNA. The original DNA remains safely in the nucleus, somewhat like the printing block in a printing press. The RNA copy is manufactured in the nucleus by transcribing just one chain of the DNA double helix (one side of the twisted ladder), which is enough to code the instructions. After additional processing, this messenger-RNA then crosses the nuclear membrane and goes out into the cytoplasm, where its instructions will be carried out by tiny organelles called *ribosomes*, the "factories" in which the protein molecules are made.

The ribosomes really are tiny: about 200 angstroms in diameter, or less than one millionth of an inch, so small that their internal structure cannot be seen even under an electron microscope. However, most cells contain thousands and sometimes even millions of them. Up to 30 separate ribosomes may be attached to a single molecule of messenger-RNA, each ribosome making its own protein as it works along the chain. Within these ribosomes, free amino acids are joined together in accordance with the sequences specified by the messenger-RNA.

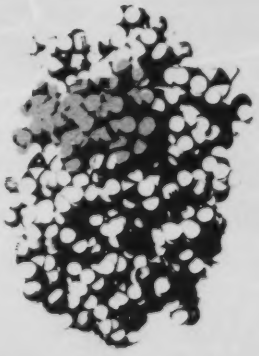
The linear sequence of amino acids in a protein is known as the protein's primary structure. However, proteins never exist as straight chains—they are always


NH3+
Lys Val Phe Gly Arg Cys Glu Leu Ala Ala Met Lys Arg His Gly Leu Asp Asn Tyr Arg Gly Tyr Ser Leu Gly Asn Trp Val Cys Ala Ala Lys Phe Asn Gln Arg Asn Thr Asp Gly Ser Thr Asp Tyr Gly Ile Leu Gln Ile Asn Ser Arg Trp Trp Cys Asp Asp Gly Arg Thr Pro Gly Ser Arg Asn Ala Val Asp Leu Cys Asn Ile Pro Cys Ser Ala Leu Leu Ser Ser Asp Ile Thr Ala Ser Val Asn Cys Ala Lys Lys Ile Val Ser Asp Gly Asn Gly Met Asn Ala Trp Val Ala Trp Arg Asn Arg Cys Lys Gly Thr Asp Val Gln Ala Trp Ile Arg Gly Cys Arg Leu
10 20 30 40 50 60 70 80 90 100 110 120 129

The primary structure of lysozyme, one of the smallest known enzymes, is this linear sequence of 129 amino acids. The primary structure determines the coiling of the peptide chains into folds and spirals (the secondary structure) and into a complex 3-D structure (the tertiary structure). The tertiary structure brings together amino acids which might otherwise be at opposite ends of the chain. In this drawing, blue circles show the amino acids which are folded together to form the enzyme's active site.



The active site of lysozyme is shown as a crevice in this 3-D model. Lysozyme digests the cell walls of bacteria that are found in nasal mucus and other secretions.



Fitting together like a key in a lock, a piece of carbohydrate from a bacterial cell wall binds to the lysozyme's active site, where it is split by amino acids on either side.

coiled—and they often contain several different but interconnected chains of polypeptides (linked amino acids). Regions of these chains coil into spirals which give the protein its secondary structure. As a result of interactions of the various side chains, the molecule as a whole then folds and coils further into a complex 3-dimensional structure, the protein's tertiary structure. The primary structure determines the secondary and tertiary structures. The tertiary structure controls function. When all the required amino acids for a specific protein are joined in a completed chain within the ribosomes, the chain is released as a free protein—and coils up into a characteristic 3-dimensional shape, on which its activity depends.

Despite their small size, ribosomes make up a large part of cells in which protein is manufactured. In the *Escherichia coli* bacteria, for instance, they account for about one-fourth of the total cell mass; this great number of ribosomes allows many proteins to be made simultaneously in one cell. It takes about a minute or two for a protein to be completed.

Ribosomes were first discovered in the middle 1950's, when biochemists became aware of these particles' role in protein synthesis at the same time that George Palade, working with an electron microscope, saw them in the cytoplasm of cells and described their gross structure. Shortly afterwards, Palade and Philip Siekevitz of Rockefeller University and other investigators isolated these particles, which were later called ribosomes.

By now it is known that ribosomes are made of two unequal sub-units, and that each of these consists of RNA and proteins. This RNA (ribosomal-RNA) differs from messenger-RNA; it is produced in the nucleolus, a prominent, globular structure in the nucleus. (A third type of RNA, transfer-RNA, is also involved in protein synthesis, particularly in bringing to the ribosomes the amino acids specified by the messenger-RNA). The ribosomes of bacteria are somewhat simpler than those of eucaryotic cells. Recently Masayasu Nomura of the University of Wiscon-

sin succeeded in taking apart the RNA and proteins in sub-units of bacterial ribosomes and then putting these components back together in the proper order, so that the sub-units functioned normally in a test tube. This was an important step towards understanding how the more complex ribosomes in human cells are made—and what happens when they malfunction.

In general, ribosomes fall into two categories: Those that are free in the cytoplasm, and those that are bound to membranes. The two kinds of ribosomes play similar roles in the manufacture of proteins. But while the free ribosomes apparently leave the proteins equally free to float in the cytoplasm, the bound ribosomes transfer their finished proteins into a gigantic, cobwebby organelle made up of membranes, the endoplasmic reticulum.

The endoplasmic reticulum.

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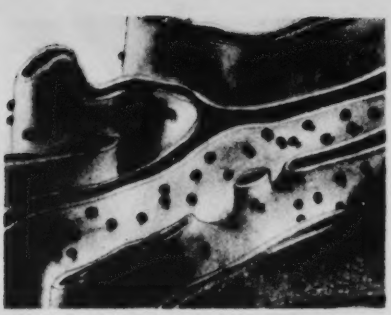

THE ENDOPLASMIC RETICULUM

In 1945, just as the electron microscope was becoming really useful as a research tool, Albert Claude of Belgium and Keith Porter at the Rockefeller Institute discovered a vast network of channels bounded by membranes in the cytoplasm of chick embryo cells. At times these looked like the layers of an onion. Porter, who is now at the University of Colorado, called this network the endoplasmic reticulum because it was more concentrated in the inner (endoplasmic) region of the cell than in the peripheral (ectoplasmic) region. Similar networks were later found in nearly all eucaryotic cells.

It turned out that the membranes of this endoplasmic reticulum (ER) all interconnect, forming a system of tubes and flattened sacs which is continuous with the nuclear membrane. In effect, this system divides the cytoplasm into two main regions: one enclosed within the "plumbing," and the other forming the outer region, or cytoplasmic matrix.

Some of these membranes are smooth (the SER). Others are "rough" (the RER), dotted with ribosomes which form granules on their outer surfaces. The outer layer of the nuclear envelope, with which they connect, also contains bound ribosomes which may synthesize special classes of proteins.

The ER's chief function appears to be the storage, segregation and finally transport of substances (mostly proteins) which the cell manufactures for use in other sections of the cell or outside the cell. These proteins are synthesized on ribosomes that are bound to the RER.

In the middle 1950's, George Palade concluded that

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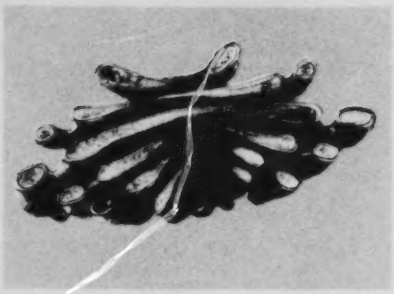
the size of the RER in a cell corresponds pretty closely to the quantity of protein which the cell exports. Plasma cells which produce antibodies have highly developed RERs with large storage cavities, for example. So do fibroblasts (connective-tissue cells) which produce collagen, and pancreatic cells which produce digestive enzymes. The gamma globulin produced by plasma cells is found mainly in these storage cavities, from which it goes forth to combat specific infections.

Cells that manufacture proteins just for their own use have little or no RER, however. In such cases, the protein is synthesized on free ribosomes and circulates freely in the cytoplasm.

While the attached ribosomes of the RER are primarily concerned with manufacturing proteins for secretion, the membrane of the whole ER synthesizes lipids (fats), including cholesterol. It is particularly well developed in certain cells where it takes on some extra function—for example, in liver cells, where it breaks down (metabolizes) drugs.

Researchers have had a hard time understanding exactly how the ER works, partly because it is impossible to isolate it intact with an ultracentrifuge—the ER simply breaks up into fragments (these are called microsomes). However, they are beginning to make some progress. Recently, for instance, Gunther Blobel of Rockefeller University discovered a "signal sequence" on messenger-RNA which determines whether the ribosomes it interacts with will attach themselves to the ER's membranes and make secretory proteins. The same sequence then leads the newly synthesized protein to storage cavities in the RER.



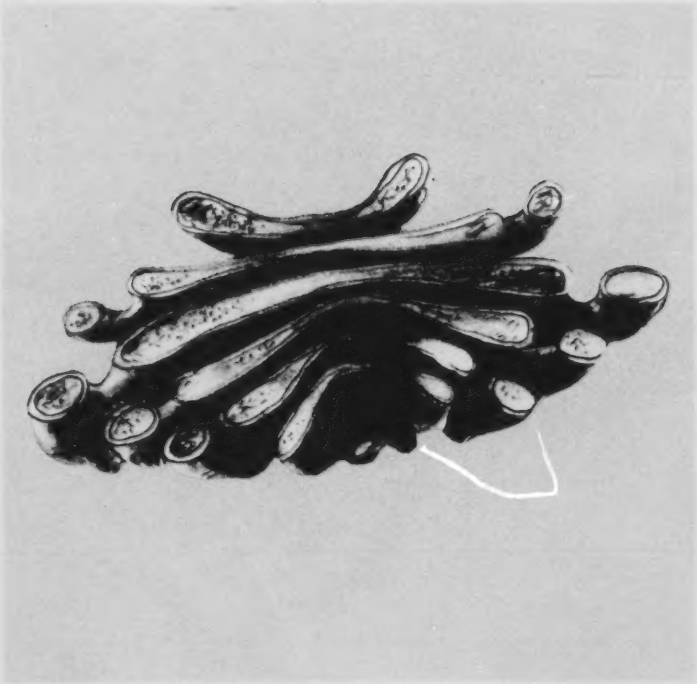
THE GOLGI APPARATUS, A PACKAGER OF PROTEIN

For a long time biologists disagreed about what it was that Camillo Golgi, an Italian scientist, had actually seen under his light microscope in 1898. Golgi had taken nerve cells from a barn owl and a cat, stained them, studied them, and noticed what *looked* like a separate structure, distinct from the nucleus, in the cytoplasm. This structure clearly took on a different color from the rest of the cell. However, some biologists thought it was just an artifact—perhaps something related to the chemicals he had used.

Half a century later, electron miscroscopists confirmed that this structure—now called the Golgi apparatus—really exists, and recently it has been shown to play a most important role in the packaging of proteins for export from the cell.

The Golgi apparatus consists of stacks of flat, membranous sacs that are piled one on top of the other. It receives molecules of protein from the ER's cavities; wraps up large numbers of these molecules into a single, membranous envelope; and sends the package on its way to the cell's surface.

The wrapping around these packages allows the cell to keep large concentrations of proteins on the ready. Some enzymes such as trypsin, which helps to break down foodstuffs in the intestinal tract, could have a disastrous effect on other proteins in the cell that made them unless they were carefully segregated or stored in an inactive form. In the 1960's, researchers showed that such enzymes (in their inactive form) are enclosed in vesicles (capsules) in the Golgi region. The vesicles then migrate

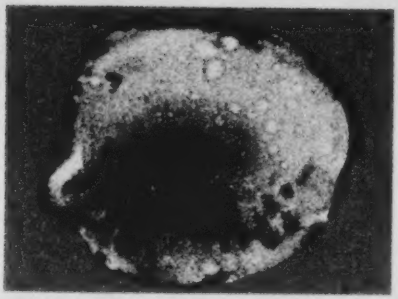


The Golgi apparatus.

to the cell's surface, where they fuse with the cell's outer membrane and release their contents. This is how cells secrete their hormones, enzymes or other types of proteins when needed.

Before packaging these proteins, however, the Golgi apparatus sometimes processes them further. It may add carbohydrates to their molecules, as it does in certain mucus-secreting cells whose Golgi apparatus is so big that it dominates the entire cell. Or it may remove part of a polypeptide chain, as in the case of insulin, which is processed from a low-activity precursor to a fully active hormone in the Golgi complex.

In addition to preparing proteins for export, the Golgi apparatus appears to be responsible for concentrating and wrapping certain enzymes into separate organelles—lysosomes—which remain inside the cell.



LYSOSOMES, THE CELL'S SCAVENGERS

When a white cell engulfs a bacterium and destroys it, the white cell's lysosomes do most of the work: They release their digestive enzymes around the engulfed material, and that is what breaks it down.

Similarly, when a cell takes in large molecules of foodstuffs, the lysosomes break these molecules down into smaller and simpler products which can be used by the cell. These products diffuse through the lysosome's membranes and go into the rest of the cell, where they serve as building blocks for various structures, until nothing is left inside the lysosome but undigestible material—and the lysosome becomes what is called a residual body. In some cells the residual body then migrates to the cell surface and gets rid of the undigested material by ejecting it into the external environment; in crude terms, it acts as the cell's garbage disposal system.

Lysosomes were discovered by a Belgian researcher, Christian de Duve, in 1949, when he homogenized (ground up) some animal cells and separated them into various fractions by running them through an ultracentrifuge.

After one of these fractions had been left standing for a few days, he noticed that the level of a certain enzyme in it rose dramatically. Since this enzyme had not attacked any part of the cells before they were ground up, he reasoned that it must have been kept segregated from the rest of the cell—probably inside some kind of organelle. He also knew that he had used a relatively gentle method of homogenization, which could have allowed the unknown organelle to remain intact; presumably it

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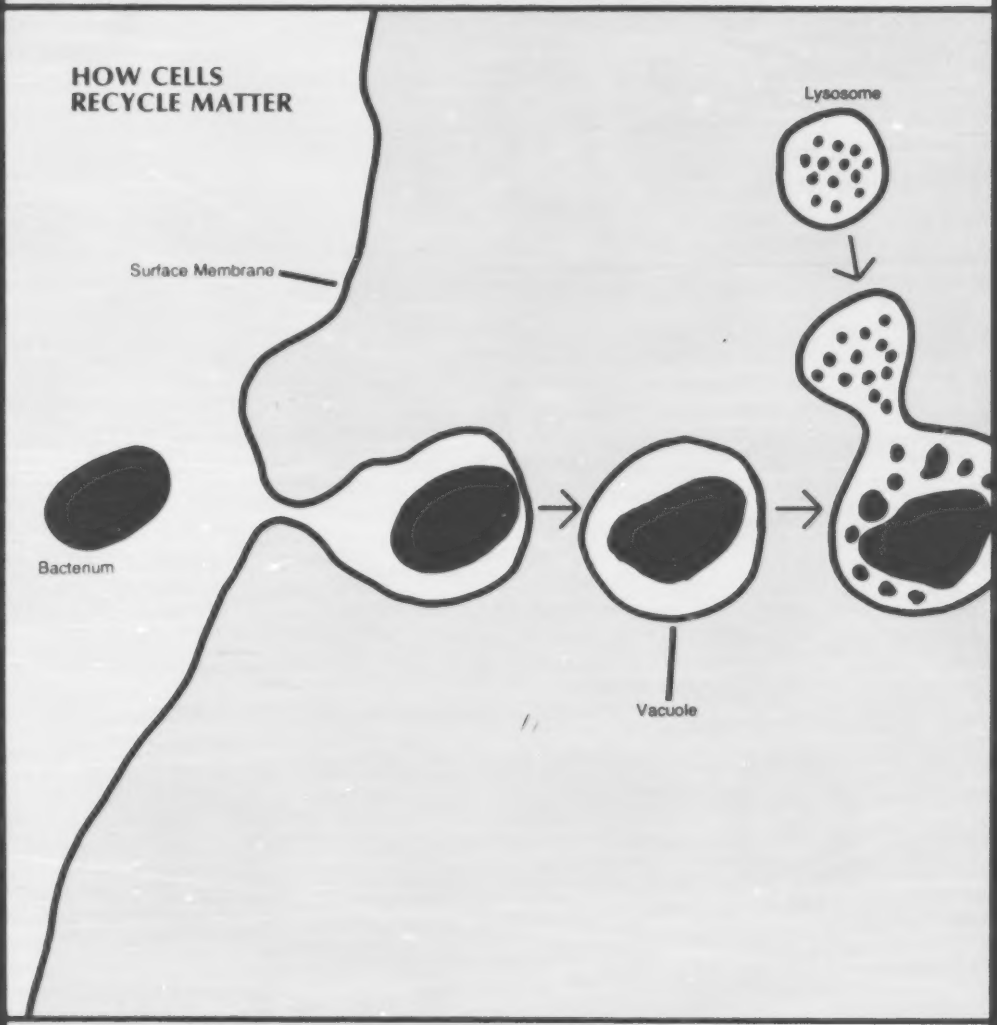
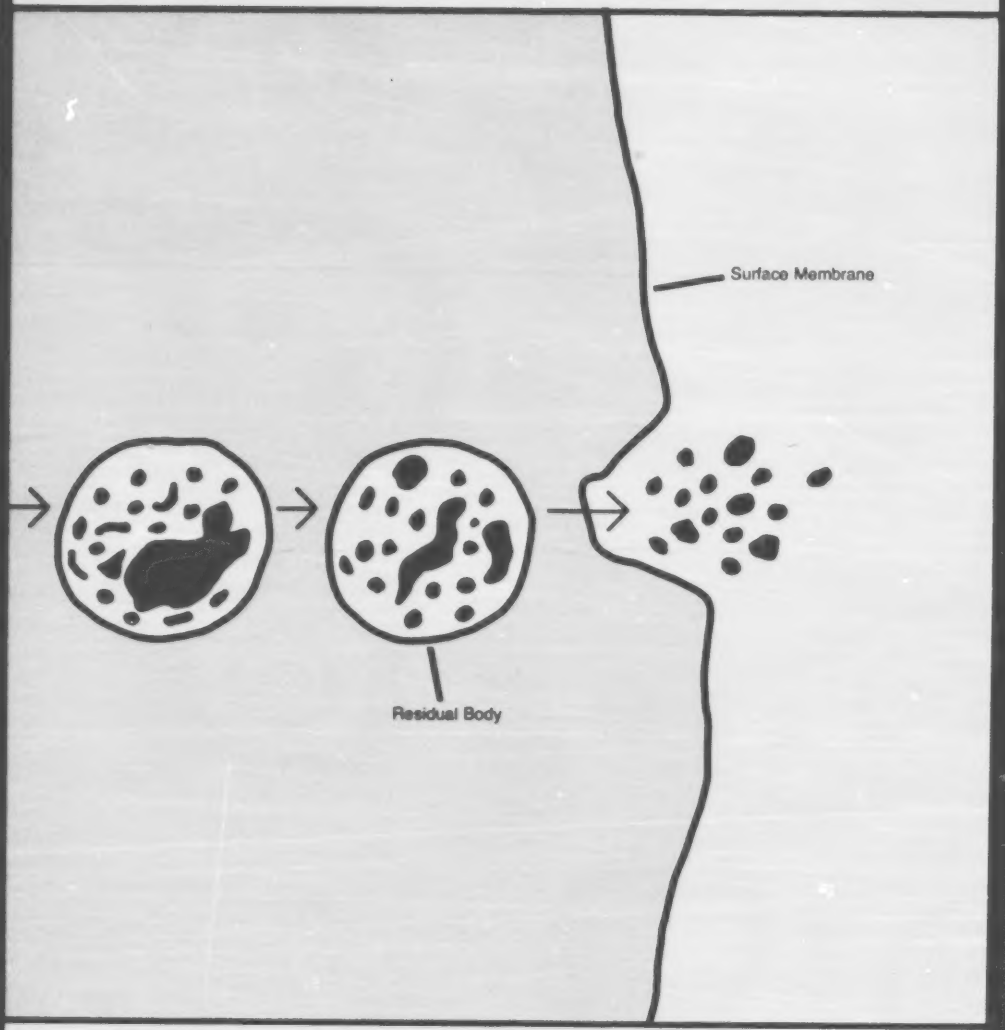


As a bacterium invades the cell, the surface membrane folds around it, forming a vacuole. A lysosome then fuses with the vacuole and releases digestive enzymes which break down the bacterium. The useful products of this

released its contents later.

De Duve's biochemical approach, for which he shared the Nobel Prize with Claude and Palade in 1974, was soon supplemented by electron microscopy. But it proved extremely difficult to identify the new particles, since they had no characteristic shape or internal struc-



digestion diffuse into the cytoplasm. Undigestible material accumulates in the vacuole, which becomes a residual body. In some cases, the residual body then migrates to the surface membrane and ejects its contents.

ture. They seemed to change size and shape constantly, according to their activity. Finally, in 1955, Alex Novikoff of Yeshiva University clearly identified some lysosomes in rat liver cells, and it is now believed that lysosomes (whose name refers to the fact that their enzymes can lyse or digest substances) exist in all animal cells. Some-

thing very similar to lysosomes also exists in plant cells.

More than 30 hereditary diseases have now been linked to the absence of various digestive enzymes in some persons' lysosomes. In each case the missing enzyme leads to the pile-up of a different kind of waste material. In Tay-Sachs disease, for instance (a disease which occurs mainly among Jews of eastern European descent), an enzyme deficiency caused by a single gene results in progressive damage to brain and other cells, and to death by the age of 4.

There is still no treatment for such "storage diseases"—diseases accompanied by an accumulation of waste materials in the victims' cells. About a decade ago, however, Elizabeth Neufeld of the NIH showed that these defects could be observed, studied and even *corrected* in a test-tube culture of cells taken from patients with these diseases. The corrective factors which she supplied were the specific enzymes which these patients' cells lacked.

This led to the idea of treating patients in a similar way, with enzyme replacement therapy. However, it was not known how the missing enzymes could be delivered to the patient's cells in all parts of his body, including his brain, nor what would induce the lysosomes in each cell to take them up. When purified enzymes are injected directly into body fluids, they tend to be quickly destroyed or inactivated, and they are not taken up by the tissues which need them most. It is particularly difficult to make such enzymes cross the blood-brain barrier—an important problem, now being investigated, since several lysosomal diseases produce severe mental retardation.

Recently Gerald Weissman of New York University developed a promising technique which may fool the white blood cells and other scavenger cells (possibly including the brain's glial cells) into accepting the missing enzyme. Mixing lipids (fatty substances) with a solution of the missing enzyme, he shook up the mixture and manufactured microscopic bubbles that contained the enzyme. Next he coated these bubbles, or liposomes,

with antibodies to make them attractive to white blood cells. When he fed these coated liposomes to Tay-Sachs cells in a test tube, he was happy to find that the white blood cells devoured the liposomes and absorbed their enzymes. Many questions remain about the potential medical use of this technique, but it may lead to an effective treatment of lysosomal storage diseases.

A different line of research has focused not on the lysosomes' deficiencies, but on the way in which these organelles guard their contents. Lysosomes are sometimes called the cell's "suicide bags" because they contain enzymes that can digest almost anything in the cell: proteins, RNA, DNA and carbohydrates. Dangerous and corrosive as these enzymes may be, they do not damage the cell itself as long as the lysosome's membrane remains intact.

When cells are programmed to die in some normal processes of embryonic development, however—for example, in the metamorphosis of insects—the lysosomes' membranes become permeable and release their enzymes to digest the cells from within. In very old cells, too, the lysosomes may release their contents, which destroy the cell.

The same kind of "autodigestion" can occur to cells that have been injured by lack of oxygen, an excess of vitamin A, exposure to certain carcinogens, or starvation. Then the lysosomes' membranes suddenly become permeable or rupture and their enzymes leak out, to digest parts of the cell.

Surprisingly, this autodigestion may be temporarily useful if the cell cannot get enough food from outside sources. The lysosomes then break down some of the cell's own contents, liberating some building blocks that can be used to make more essential substances and ensuring the cell's survival without major damage. At other times, however, the rupture of lysosomal membrances may cause the cell's death.

The inflammation and pain of arthritis may also be related to a leakage of lysosomal enzymes from certain

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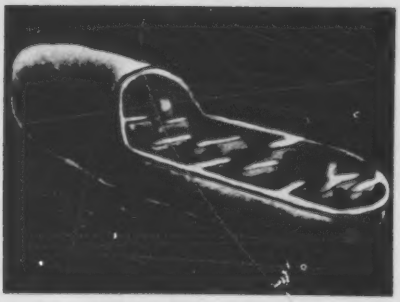
white blood cells. (This link is supported by the fact that substances which reduce inflammation, such as cortisone, are known to strengthen the lysosomal membranes).

In many ways, then, health and disease depend on the lysosomal membrane's ability to control the release of its contents. Some substances seem to stabilize and strengthen this membranous envelope, while others weaken it. In the future, researchers may find ways to use these properties for the prevention of disease or for therapy.

This is still a long way off, however. At present, much remains to be learned about how and where lysosomes are made (some lysosomes appear to come from the Golgi apparatus, others from the ER), what stages they go through, and what controls their activities.

A mitochondrion.



MITOCHONDRIA, THE CELL'S POWER PLANTS

For thousands of years, men puzzled over the question of where body heat comes from. This heat was recognized as nearly synonymous with life itself—but what produced it? The source of the energy of man or beast was equally mysterious.

In recent decades it has become clear that both heat and energy can be traced to some sausage-shaped organelles in our cells, the mitochondria.

Of course the ultimate source of energy for all plants and animals is sunlight. But the sun's energy can be harnessed by plants, through photosynthesis, and stored in molecules of carbohydrates. When animals eat these carbohydrates and break them down to carbon dioxide and water, with the help of oxygen and an arsenal of enzymes, large amounts of energy become available. Animals immediately convert this energy into molecules of high-energy ATP (adenosine triphosphate)—the universal currency of energy in living things. Excluding only the very first stages in carbohydrate breakdown, which are called glycolysis, the entire, complicated process of energy transfer to ATP takes place within the mitochondria.

Mitochondria are the largest organelles in the cell, after the nucleus, yet some cells have more than a thousand of them. Thin and long, they vary in diameter from 0.5 to 1 micrometer and in length up to 7 micrometers. Their thread-like outlines can be seen with a good light microscope. Although they were first observed in 1850, it took a century to visualize their internal structure and understand their function.

Actually the story goes back even further, to the 18th century, when Lavoisier showed that animals require oxygen for respiration. This led chemists to study cellular respiration, the process by which living cells use oxygen to release the chemical energy stored in foodstuffs. Early in the 20th century biochemists discovered that these reactions fall into two major groups: (1) The carbon pathway (including the Krebs citric-acid cycle, named after Hans Krebs of England), where a series of chemical reactions, each requiring a specific enzyme, breaks down the carbohydrates into carbon dioxide and hydrogen; and (2) the hydrogen pathway, which transfers the hydrogen to oxyen in stages, forming water and releasing energy.

The whole process is organized much like an assembly line. In the hydrogen pathway, the hydrogen's electrons pass through an "electron transport chain" made up of enzymes that act as carriers, and as the electrons move from enzyme to enzyme, they give up part of their energy, which is stored in molecules of ATP. The iron-containing enzymes, cytochrome a, b and c, carry out the final stages of the process. All in all, three molecules of ATP are formed for every atom of oxygen that is used up in respiration.

For a long time, biochemists studied these reactions in cell extracts without worrying about what parts of the cells might be involved. One scientist, B.F. Kingsbury of Cornell University, did suggest that mitochondria might be the site of cellular respiration back in 1912, but this was ignored.

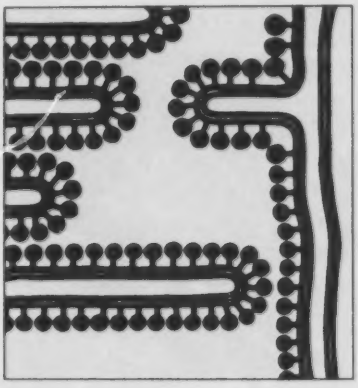
In the 1940's, using an ultracentrifuge, Albert Claude and his associates isolated various cell particles including mitochondria. Shortly afterwards, in 1948, Albert Lehninger of Johns Hopkins and Eugene Kennedy of Harvard showed that the reactions leading to the synthesis of ATP occurred in the mitochondria.

In the early 1950's, Palade and the Swedish scientist Fritiof Sjostrand reported that mitochondria are bounded by a membrane and that they have a system of parallel, regularly spaced inner ridges which were named cristae.

It is now clear that there are, in fact, two membranes around the mitochondria of plants, protozoa, molluscs, insects and man: an outer membrane, set off by a fluid-filled gap; and an inner membrane which is folded inward at various points to increase its surface, forming the cristae, so that the enzyme molecules of the electron transport chain, which are attached to this inner surface in specific sequences, can be packed more densely side by side in the mitochondria.

This general design for mitochondria seems to have existed unchanged, through the evolution of plants and animals, for more than 1.2 billion years.

Though mitochondria are generally visualized as oval-shaped, they can change shape quite drastically. They swell and contract in response to various hormones and drugs. Even in very low concentrations, Lehninger found, the thyroid hormone thyroxin will make mitochondria swell and will simultaneously "uncouple" the electron transport chain from the synthesis of ATP, so that even though carbohydrates may be metabolized and oxygen consumed, no ATP will be manufactured. ATP, on the other hand, makes mitochondria contract. This swelling and contraction appear related to the movement of water



Based on a drawing by George Palade, this diagram shows the intricate internal structure of a mitochondrion, with outer membrane and particles on the folded inner membrane, part of which forms the cristae.

in, out and through cells, which is of particular importance in the kidney.

The more scientists learn about mitochondria, however, the more their curiosity is aroused, for these are without a doubt the strangest of the cell's organelles.

To begin with, mitochondria contain their own hereditary material (DNA), which resembles that of bacteria far more than that of animal cell nuclei. Because of this similarity, many scientists believe that mitochondria are derived from bacteria that infected a primitive cell and evolved into a useful symbiotic relationship with it.

As Lewis Thomas puts it, "A good case can be made for our nonexistence as entities... We are shared, rented, occupied. At the interior of our cells, driving them, providing the oxidative energy that sends us out for the improvement of each shining day, are the mitochondria, and in a strict sense they are not ours. They turn out to be little separate creatures, the colonial posterity of migrant procaryotes, probably primitive bacteria that swam into ancestral precursors of our eucaryotic cells and stayed there. Ever since, they have maintained themselves and their ways, replicating in their own fashion, privately, with their own DNA and RNA quite different from ours. They are as much symbionts as the rhizobial bacteria in the roots of beans. Without them, we would not move a muscle, drum a finger, think a thought."

"My mitochondria comprise a very large proportion of me. Looked at in this way, I could be taken for very large, motile colony of respiring bacteria, operating a complex system of nuclei, microtubules and neurons for the pleasure and sustenance of their families, and running, at the moment, a typewriter," continues Thomas somewhat facetiously. "I am...obliged to do a great deal of essential work for my mitochondria. My nuclei code out the outer membranes of each, and a good many of the enzymes attached to the cristae must be synthesized by me. Each of them, by all accounts, makes only enough of its own materials to get along on, and the rest must come from me. And I am the one who has to do the worrying."

During the past few years, scientists have begun to learn which proteins and enzymes of the mitochondria are synthesized according to directions in the mitochondrial DNA, and which are controlled by the genes in the nucleus. This information would be of considerable importance for the design of antibiotics and drugs, as well as for the understanding of genetic diseases. For example, researchers have found that chloramphenicol—a powerful antibiotic which can cause a fatal anemia—interferes with the synthesis of mitochondrial DNA, while other antibiotics do not.

Mitochondria are just as important to the life of each cell as the heart is to the human body. At least 95 percent of our cells' energy comes from mitochondria. (Only the mammalian red blood cells, which have no nuclei, get along without mitochondria; they obtain whatever energy they need from the partial breakdown of glucose in their cytoplasm). Growing cells continuously synthesize nucleic acids, proteins, and other components, for which they need the energy that is stored in molecules of ATP. Muscle cells which carry out mechanical work, plant cells which pump water against the force of gravity, and many other cells also require a continuous source of energy.

Besides supplying this energy, mitochondria apparently help to control the concentration of water, calcium and other ions in the cytoplasm. They are also deeply involved in the breakdown and recycling of sugars, fatty acids and amino acids to recover their energy, as well as in the formation of urea as a waste product, to be excreted through the kidney.

These strange organelles may thus hold clues to a variety of seemingly unrelated diseases. They have been linked to some liver diseases (e.g., viral hepatitis, obstructive jaundice and cirrhosis of the liver); some muscle diseases (e.g., familial myotrophic dystrophy); and some kidney diseases. In all these conditions, pathologists have seen large amounts of materials pile up inside the mitochondria as "inclusions" of varying shapes and sizes,

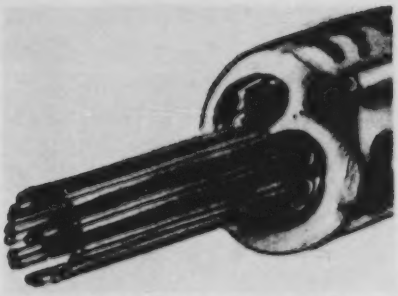
presumably waiting to be processed. What these inclusions consist of remains a mystery, but if scientists could find out, they might discover which specific components (for instance, enzymes) are involved in each disease.

In addition, several calcium disorders may be related to mitochondrial defects. For example, abnormal concentrations of calcium (possibly caused by malfunctioning mitochondria) may lead to arthritis, bursitis, or arterial disease.

While all these leads are promising, the greatest spin-off from research on mitochondria may be in the area of energy—not only for the cell, but for general use by mankind.

As the oil crisis has made us realize, we presently depend on a limited supply of fossil fuels—coal and oil—which are of biological origin but cannot be replenished. On the other hand, nature contains a far greater resource: a molecular know-how and technology gained over millennia, by which biological systems manufacture ATP from solar energy. This technology awaits us. It exists in very similar, if not identical forms in mitochondria and in their mirror image, the chloroplasts, which are found in green plants, where they do the work of photosynthesis, converting the sun's energy into carbohydrates. Like mitochondria, chloroplasts have an outer and an inner membrane. They have some of their own DNA. They, too, may have originated as some kind of infection, probably with blue-green algae. And it is on chloroplasts that we ultimately depend for nearly all our energy—that of our bodies as well as that which is stored in deposits of oil and coal.

If scientists ever unravel the details of the process by which chloroplasts store solar energy in carbohydrates and mitochondria release it, we may be able to produce unlimited quantities of usable energy.



MICROTUBULES, THE CELL'S PHYSICAL PROPS

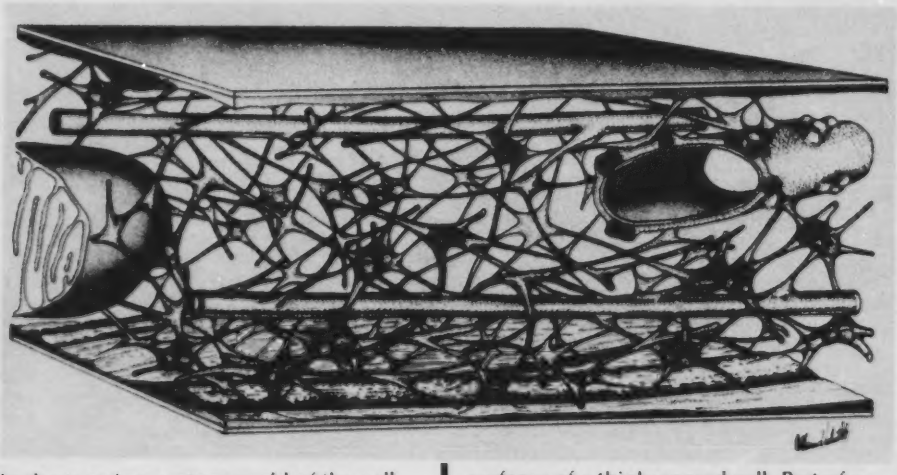
All the organelles described so far are bound by membranes. For a long time, the rest of the cytoplasm—a liquid called the cell sap, or ground substance—appeared totally unstructured. But as scientists learned to use newer and gentler fixatives to prepare cells for electron miscroscopy, more and more tiny structures materialized in this soup.

The most prominent of the new structures are two organelles which provide an intricate system of physical support for the cell—the equivalent of buttresses or skeletal bones—as well as a contractile mechanism for cell movement: microtubules and microfilaments. Neither is bound by a membrane.

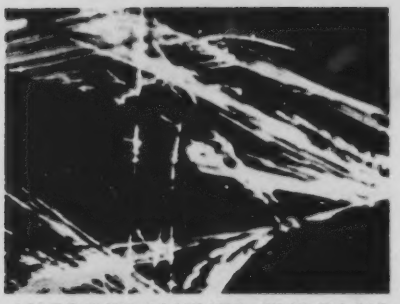
Microtubules were first noticed in the middle 1950's, but they were seen only rarely until the development of glutaraldehyde as a gentle fixative in 1963. Extremely thin cylinders, about 200 to 300 angstroms in diameter and of variable length, microtubules are constructed chiefly of proteins called tubulins. In 1967, Edwin Taylor and his associates at the University of Chicago discovered that colchicine—a chemical used to arrest cell division—did its work by binding to the protein tubulin. This pointed to the role of microtubules in mitosis, and helped to answer a question which had worried generations of biologists: How do chromosomes sort themselves out into two sets and separate during cell division? The details of mitosis would have been very hard to explain without understanding the chemistry of the spindle fibers which organize this separation. In fact, if there were no microtubules, scientists would have had to invent them. Something of

this sort was needed to account not only for mitosis, but for the surprisingly firm structure of such seemingly vulnerable fibers as the long, thin axons of nerve cells, as well as for the unique structure of some red blood cells, which are held in a disc-like shape by hoops composed of microtubules.

Microtubules are also involved in assisting the transport of substances in and out of the cell and in the motion of cells themselves. They make up the cilia and flagella, whip-like filaments which project from the surface of cells and move rhythmically. Large numbers of cilia are found on cells that line the respiratory system, for instance, where they help to sweep out dust and debris. Both cilia and flagella play an important role in human reproduction: the coordinated beating of cilia in the oviduct produces a sort of current which draws the female's egg into the uterus, while the rapidly thrashing tail of sperm actually is a flagellum.



In the teeming, watery world of the cell, where organelles move about rapidly, microtubules play an important role as physical props, and microfilaments form a lattice which encloses them. This model shows Keith Porter's view of the space between the upper and lower surfaces of a thinly spread cell. Part of a mitochondrion can be seen at left, and a section of rough endoplasmic reticulum at the upper right. Ribosomes are enmeshed in the lattice. Two long, cylindrical microtubules are at top and bottom.



MICROFILAMENTS, THE BASIS OF CELL "CRAWL"

The movement of living cells has fascinated biologists ever since Leeuwenhoek discovered "tiny animalcules prettily a-moving" under his simple microscope. But for a long time, scientists' efforts to study such movements were stymied by techniques which required killing cells before they could be examined under the microscope. It is only since the development of time-lapse photography, together with the phase-contrast and interference microscopes, that researchers have been able to study cells while they were moving.

There seem to be two main kinds of cell motion: That produced by the rhythmic beating of special structures on the cell surface (such as cilia and flagella) and that connected with some wispy organelles inside the cell, microfilaments. The action of these microfilaments allows cells to "crawl" along surfaces by forming extensions, called pseudopods, towards which the bulk of the cytoplasm flows. While the precise nature of this movement is not understood, it seems to involve the continual transformation of the liquid parts of the cytoplasm (the cell sap, or ground substance) into a viscous gel with the help of calcium, and its subsequent dissolution into a liquid again. Amoebae, white blood cells, macrophages, and the tips of growing nerve cells "crawl" in this fashion. So, probably, do cancer cells.

Microfilaments apparently consist of thin strands of actin, a protein. Actin has been studied for nearly half a century in muscle cells. In the fifties scientists learned, primarily through the work of Hugh Huxley at the Medical Research Council laboratories in England, that contraction

in the skeletal muscles is produced by the sliding of thin filaments of actin between thick filaments of another protein, myosin. But it is only in the past 15 years that researchers have found evidence of similar actin-myosin interactions, involving microfilaments, in many other kinds of cells. The whole process of secretion, as when cells discharge hormones, enzymes or other proteins, may depend on such interaction. So may the movement of many cells which help to defend the body against invading organisms.

As the President's Biomedical Research Panel put it recently, "Here again is a striking example of biological versatility and—with it—the promise of a common key to the solution of many problems in basic or applied biomedical sciences."

Current research on all the cell's organelles—studies of the nucleus, ribosomes, ER, Golgi, lysosomes, mitochondria, microtubules and microfilaments—holds such promise. However the common key that may unlock the greatest number of health benefits may well be found in the cell's filmy membranes, particularly in the plasma membrane at the surface of the cell.

"The cell membrane is not a wall or a skin or a sieve. It is an active and responsive part of the cell; it decides what is inside and what is outside, and what the outside does to the inside." **Daniel Mazia, University of California, Berkeley.**

MEMBRANES, THE CELL'S TOUGH, DELICATE GUARDIANS

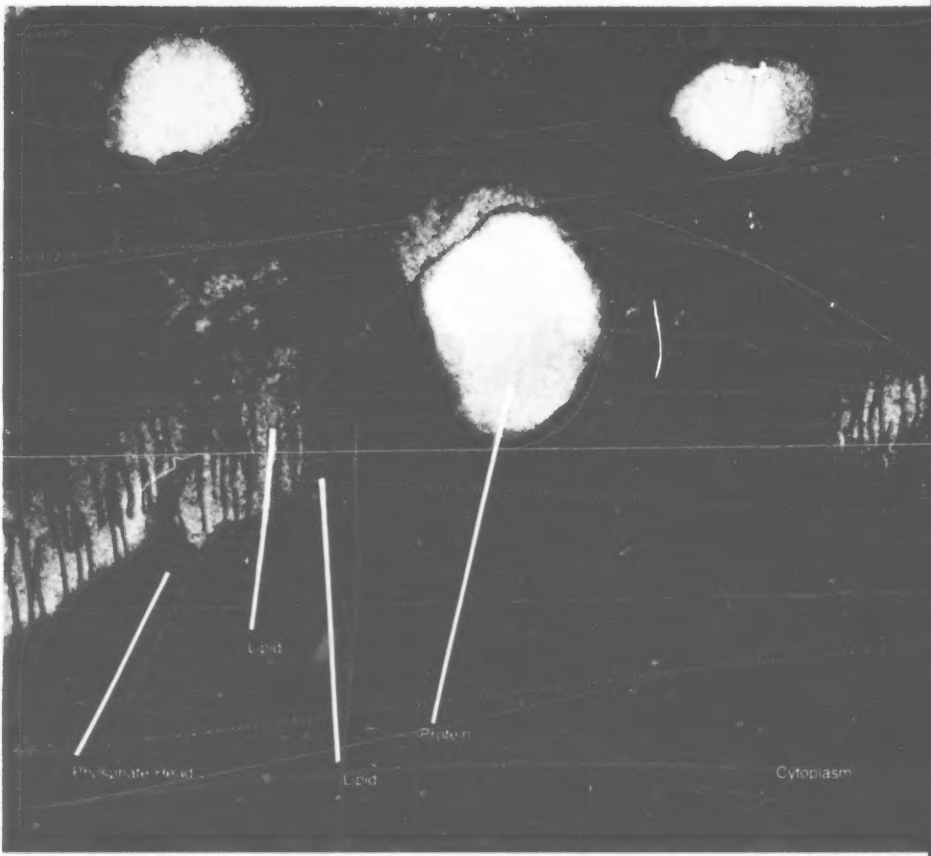
"In the beginning," writes Gerald Weissman, "there must have been a membrane! Whatever flash of lightning there was that organized purines, pyrimidines, and amino acids into macromolecules capable of reproducing themselves, it would not have yielded cells but for the organizational trick afforded by the design of a membrane wrapping." He visualizes a kind of bubble in which the first macromolecules must have been enclosed, to protect them from being dissipated or dissolved in the strong salt of the early sea.

Membranes are now arousing enormous curiosity among biologists because it has become clear that these diaphanous films, less than 100 angstroms (1/100,000th of a millimeter) thick, control some of the most vital functions of the living cell. Furthermore, there are layers upon layers of them, in and around various organelles.

The double-membrane envelope which forms a channel around the nucleus not only protects the genetic material but also connects with the "plumbing"—the system of membranous tubes, folds and compartments—which makes up the rough and smooth endoplasmic reticulum and the Golgi apparatus. The membrane-covered mitochondria contain a separate inner membrane system of their own. And at the surface of the cell, the all-powerful plasma membrane—an organelle in its own right—stands between the cell and the world.

Like the skin that covers our bodies, the plasma membrane creates a separate environment within which the biochemical processes of life can take place. In addition, it controls everything that goes in or out of the cell.

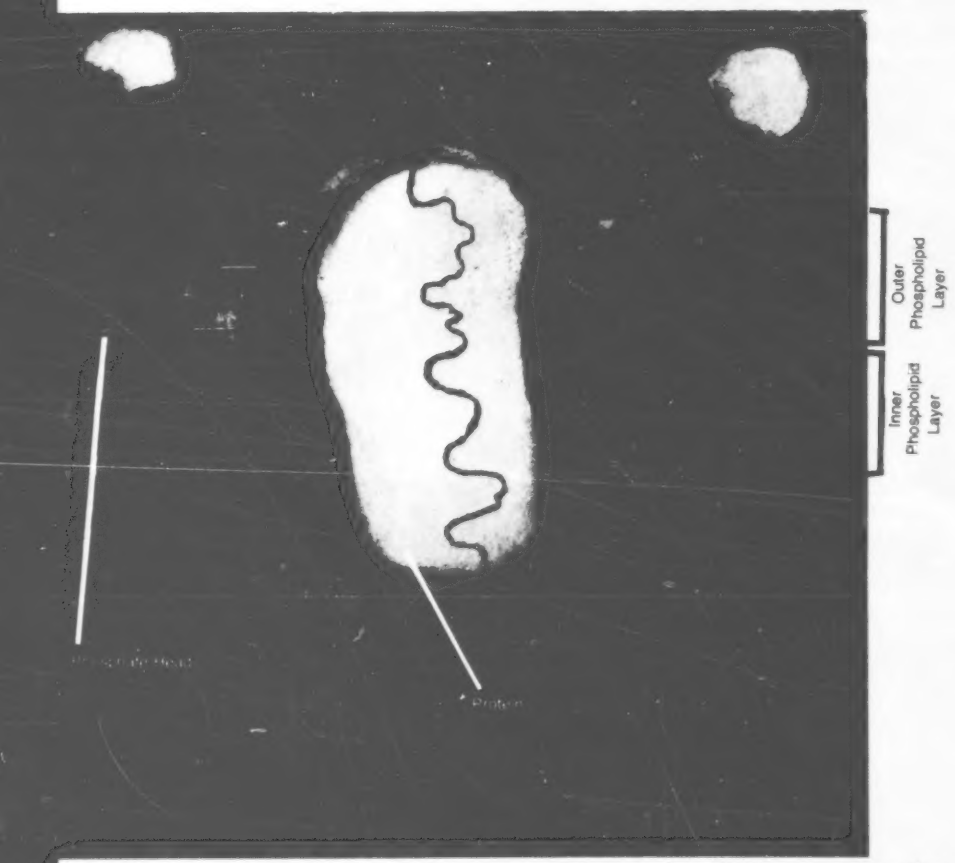
It also receives signals from other cells, interacts with them to form tissue, recognizes attacking viruses, responds to hormones. And as a result of its contact with the outer environment, it probably tells the nucleus when to divide—or when to stop. Despite its fragility, it is a tough



The plasma membrane, as visualized by S.J. Singer, consists of two layers of phospholipids with proteins floating in them like icebergs. The phospholipids are arranged so that their water-loving phosphate heads face outwards, either towards the cell's outer environment or towards the watery cytoplasm inside the cell. As a result, the insoluble lipids make up the center of the membrane.

and resourceful guardian of the cell's interior.

The secret of the membranes' power lies in their ingenious composition and structure. After years of puzzlement and speculation, biologists now have some idea of how these thin membranes are organized.



Some of the proteins that float in the phospholipid layers remain on the surface of the membrane and are relatively easy to detach. Others, like those shown here, extend part-way or all the way through the membrane. The proteins serve as receptors for specific hormones, neurotransmitters and antibodies, as well as "pores" or gates for substances entering the cell.

Of course there is no "typical" membrane, since the various types that exist within each cell and in different kinds of cells differ in composition and function. Furthermore, any particular membrane is likely to change from moment to moment, in response to its environment. Nevertheless all cell membranes follow the same general pattern.

Their first task is to provide effective compartments. Since cells live in a watery environment and also contain a large amount of watery fluid, in which the organelles float, anything which forms a compartment must be pretty water tight. In fact, membranes have been found to consist mostly of lipids (fat) interspersed with proteins, and since fat and water don't mix, this creates an efficient barrier to keep foreign substances out and water in. Substances that dissolve well in lipids will not dissolve well in water, and vice versa (excepting only detergents and gases, such as oxygen and nitrogen, which dissolve in both).

A membrane is not just a layer of fat, however, but an intricate, elastic and fluid "bilayer" consisting of two layers of phospholipids (each layer one molecule thick) interspersed with proteins which are either embedded in the lipid layers or loosely attached to their surface. The two layers of phospholipids arrange themselves very neatly, as described in 1938 by James Danielli, who was then at the State University of New York at Buffalo: The part of the phospholipid molecule which is water-loving (a small portion containing charged phosphate, which is electrostatically attracted to water) faces out towards the outside world, or towards the watery cytoplasm, while the rest of the molecule (consisting of hydrocarbons, which are insoluble in water) is pushed to the center of the membrane.

Actually the layer of membrane which faces the outside world fulfills quite different functions from the layer which faces the cytoplasm. Therefore the two layers are not symmetrical; each consists of a different array of lipids and proteins.

MEMBRANE PROTEINS—ICEBERGS IN A SEA OF LIPIDS

In 1966, S.J. Singer of the University of California at San Diego proposed a "fluid-mosaic" model for cell membranes. He compared some of the proteins in cell membranes to "icebergs floating in a sea of lipids," and said that their movement would create an ever-changing "fluid-mosaic" pattern. In his view, most of these proteins are folded up so as to have one hydrophobic (water-hating) and one hydrophilic (water-loving) end—just as do the phospholipid molecules, though of course the proteins are much larger. He also suggested that if the proteins are large enough to span the entire thickness of the membrane, they must have two hydrophilic ends (which protrude) and a hydrophobic middle (which is embedded in the phospholipid layer). Although such tri-partite proteins were unknown at the time, they have been found to exist in membranes.

The proteins in membranes are extremely important because they do most of the specialized work, while the lipids serve largely as a diffusion barrier.

In the plasma membrane, for example, protein "receptors" respond to specific hormones, neurotransmitters and antibodies. They selectively accept specific chemicals from outside the cell, which must fit them as precisely as a key in a lock, and send appropriate signals into the cell's interior.

The receptors on which so much depends must make exquisitely refined discriminations at every phase of the cell's life, beginning with fertilization. For instance, sperm cells recognize egg cells only when these belong to the same or to a very closely related species. As George

Palade puts it, "Imagine what problems could arise for all the creatures that live in the sea, with all kinds of eggs and all kinds of sperm floating around in the water! Yet because of the precise information obtained through receptors on the cell membranes, fertilization occurs only within specific species." The intricate process of differentiation, through which embryonic cells take on specialized functions, also depends largely on specific cells' recognizing one another through the proteins in their plasma membranes.

The failure of protein receptors to do their job properly may lead to a variety of diseases. "We are beginning to understand that there may be either inherited or acquired defects in the organization of cell membranes," says Palade, who now directs the Center for Research on Cellular Membranes which NIGMS started at Yale University in 1974. "For example, an organism may produce enough of a hormone, such as parathormone or insulin, but not have enough receptors for it in the membrane of the target cell. This may look like a hormone deficiency, when in fact it is not. We are finding many membrane disturbances of this sort. Or there may be an excess of receptors on the membrane of the target cell, leading to a syndrome that mimics the overproduction of a hormone or neurotransmitter; for example, some forms of hypertension and cardiovascular disease may be produced by an excess of receptors for hormones on the membranes of smooth-muscle cells on the arterial walls."

"We have a great deal of optimism and excitement today because we think that the cell surface is the key to understanding cancer as well as many other diseases." **Gerald M. Edelman, Rockefeller University.**

DIRECTING TRAFFIC ACROSS THE PLASMA MEMBRANE

As primary guardian of the cell's gates, the plasma membrane is responsible for keeping the chemical composition of the cell's interior constant within very narrow limits. The interior of the cells of higher animals needs to be high in potassium ions and low in sodium ions, for instance, while their exterior environment—blood and body fluids—has the reverse concentration, being high in sodium (like sea water) and low in potassium. This creates a difference in electrical potential of about one-tenth of a volt or higher across the cell membrane, which is particularly important to the action of nerves and muscles. Scientists are only beginning to understand how the plasma membrane accomplishes such impressive feats.

The simplest traffic across the plasma membrane is *passive transport,* which requires no energy. The molecules diffuse through the membrane at rates determined by their solubility in lipids, their size, and differences in their concentration. Those that are highly soluble in lipids move most rapidly. Water and other small molecules which are not soluble in lipids can also diffuse through the membrane, with the smallest ones passing through at the highest rate. (If there were no membrane at all, however, water could diffuse in or out of the cell 100,000 times more rapidly. It is believed that there are "channels" or "pores" across the lipid layer through which water can move freely; if so, the total area of these channels must be 100,000 times smaller than the total area of the cell surface). In each case of passive transport, the molecules diffuse from a space where their concentra-

tion is low, until it is equal on both sides of the membrane.

With sodium and potassium, however, some mechanism actually moves ions in and out of the cell against the concentration "gradients." This *active transport,* which maintains a high concentration of potassium and a low concentration of sodium within the cell, despite opposite conditions on the other side of the membrane, requires the expenditure of energy. And the energy comes from the cell's universal fuel, ATP. The plasma membrane contains certain enzymes which split the chemical bonds of ATP and then use the energy to carry potassium in and sodium out of the cell. The amount of energy involved is surprisingly high: It has been calculated that up to 18 percent of the total ATP required by the brain, for instance, is expended in such activities.

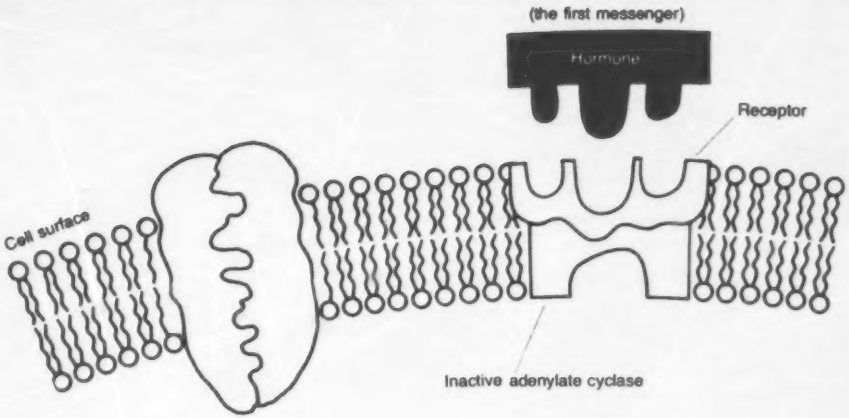
A third type of traffic across the plasma membrane involves the release or uptake of various substances whose molecules are too big to cross the membrane either by diffusion or through pores. Instead, they travel in membranous packages. In protein-secreting cells, for instance, new proteins are wrapped in pieces of membrane in the Golgi apparatus, forming vesicles; the vesicles then move to the cell's surface, where their membranous envelope fuses with the plasma membrane and their contents are dumped outside the cell. This is called *exocytosis.* In a reverse process, *endocytosis,* proteins or other molecules from outside the cell attach to the cell's plasma membrane, which folds in to envelop them; this forms small vesicles which move into the cytoplasm, carrying drops of extra-cellular medium with the substance to be used inside the cell. In all of these cases, matter is brought into the cell or discharged from the cell without interrupting the continuity of the plasma membrane. Something similar occurs during fertilization, when the sperm's plasma membrane fuses with the egg's plasma membrane in such a way that the sperm nucleus can enter the egg without any exposure to the surrounding medium.

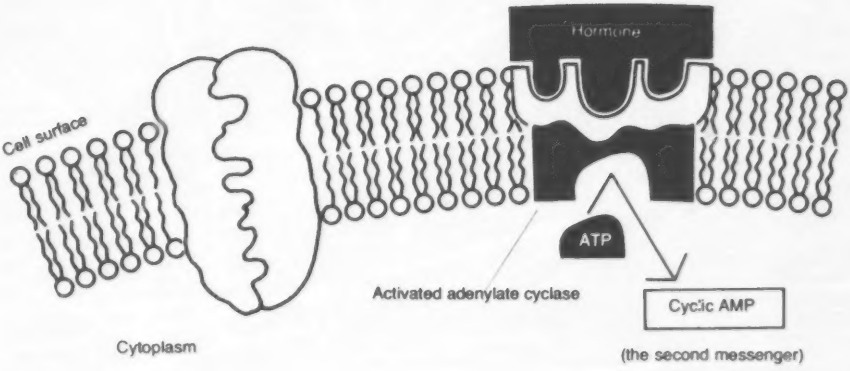
Besides directing traffic in and out of the cell in all these ways, the plasma membrane controls the cell's communications system, receiving signals from the outer environment (including signals from other cells) and sending out messages of its own.

Some of these signals are carried by the chemical messengers called hormones, which circulate in the bloodstream with instructions to cells in many parts of the body. As these hormones reach each target cell, they generally do not enter it, but trigger intricate responses. Only a few hormones, such as the steroids (including cortisone and the sex hormones) which are derived from cholesterol and thus easily soluble in fat, can actually pass through the cells' membranes. Most hormones, for instance insulin and some neurotransmitters, act by giving signals to specific receptors on the cell surface; these receptors then activate a second-messenger system which orders appropriate changes within the cell.

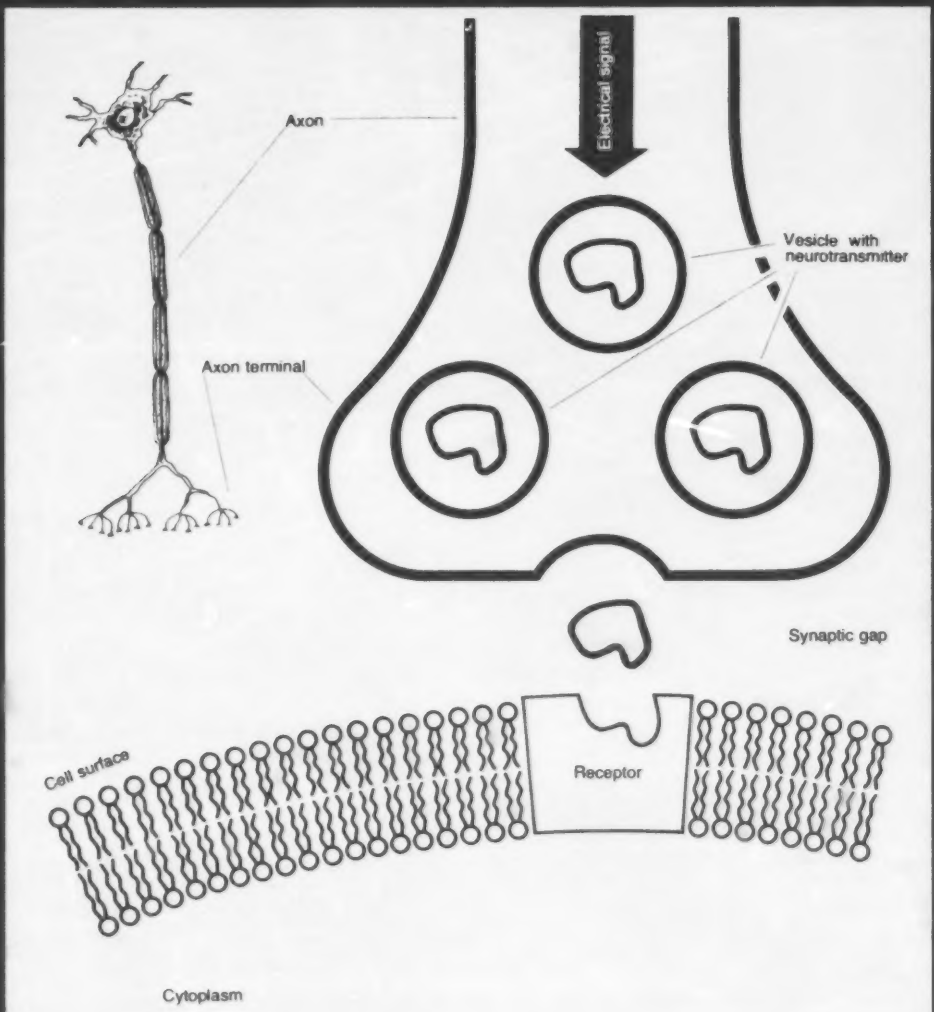
Earl Sutherland of Vanderbilt University discovered how this second-messenger system works and won the Nobel Prize for it. He found that adenylate cyclase, an enzyme in the plasma membrane of many cells, can be activated to convert ATP (the universal currency of energy in cells) into cyclic AMP, a nucleotide which is then released into the interior of the cell. Thus, when a hormone (the first messenger) binds to a specific receptor on a cell surface, it triggers the dispatch of cyclic AMP (the second messenger) to the cell's biochemical machinery. Another cyclic nucleotide which acts in similar fashion, cyclic GMP, has been identified, and recently scientists discovered yet a third type, cyclic CMP.

It is now clear that these second messengers regulate hundreds of diverse processes in living cells. The surge of energy which we sometimes feel under stress (as a result of the conversion of stored glycogen into glucose); the discharge of secretory products from cells; the activation of dormant genes; and even contact inhibition—all depend on the action of a second messenger on different components of different cells. The second-messenger





The "second-messenger system" involves a hormone (the first messenger) which fits a specific receptor on the cell surface. When the hormone binds to the receptor, it activates an enzyme (adenylate cyclase) which then converts some ATP from the cytoplasm into a nucleotide (cyclic AMP) which acts as the second messenger and releases a specific signal to the interior of the cell.



The nervous system depends on the rapid transmission of nerve impulses across the tiny spaces—the synaptic gaps—between one neuron and the next. These gaps are crossed by chemical neurotransmitters. In this drawing, an electrical signal travels down to the tip of a nerve cell's axon, causing vesicles which contain units of a neurotransmitter to fuse with the plasma membrane and release their contents into the synaptic gap. The neurotransmitter then binds with a specific receptor on the plasma membrane of the next neuron, changing its electrical potential.

system is involved in so many diseases, in fact, that substances which facilitate or inhibit it are expected to prove very useful in medicine in the future.

Hormonal messages travel far and wide in the body via the bloodstream; they can be recognized by very distant organs, but they may take hours, days or weeks to produce their complex effects. In order to stay alive, animals must have a much quicker means of response, with which they can react to events within seconds or milliseconds. This is where the nervous system comes in. When you touch a hot stove, look or listen, the information is carried almost instantaneously by neurons (nerve cells) which, unlike most other cells, produce electrical signals in response to physical or chemical stimuli. The neurons' plasma membranes play a key role in this transmission. One common sequence is as follows: An electrical signal travels down the surface of a neuron's thin axon (a long fiber); this induces vesicles which contain units of neurotransmitter to fuse with the plasma membrane at the terminal of this axon, and to release their contents into the synaptic cleft (the gap between this neuron and the next cell). If enough of the newly released transmitter reaches the plasma membrane of the next neuron, it changes the membrane's electrical potential, producing a new nerve impulse which then repeats the whole process. If, on the other hand, enough transmitter reaches the plasma membrane of a muscle cell at a special region called the neuromuscular junction, it stimulates the muscle to contract.

"I find it somewhat mind-boggling that the cell membrane can undergo such constant and rapid reconstruction, while at the same time retaining its physiologic identity: its characteristic functions of compartmentalization, organization and interaction." **Leonard Warren, University of Pennsylvania.**

NEW TOOLS WHICH OFFER A NEW VIEW OF MEMBRANES

As important and powerful as the plasma membrane is, it makes up only a fraction of the total amount of membrane in a cell. Most animal cells, especially those that have specialized functions, are so packed with membranes that there may be 50 to 100 times as much membrane inside them as on their surface. (In plant cells the proportion of inner membrane is even greater, going up to 150 times the amount of membrane on their surface). Yet the plasma membrane is best known to scientists. The main problem in studying membranes has been the difficulty of obtaining pure specimens. Until recently, this was possible only with the plasma membrane of the mammalian red blood cell, which has no nucleus.

When biochemists grind up cells and centrifuge their components, only fragments of the cells' membranes can be recovered—usually in the form of small, closed vesicles or ragged pieces of unidentified origin. These can be sorted out and identified, so that by now the membranes of practically every organelle can be isolated, but they still vary in purity. Such brutal treatment is not necessary with the mammalian red blood cell, however. Since it contains mostly hemoglobin and has neither nucleus nor mitochondria, nor any internal membranes, it can be emptied with relative ease: It is simply induced to swell up until temporary, large pores open in its plasma membrane, letting the fluid and hemoglobin seep out. The plasma membrane is then allowed to shrink back to its normal size and the pores close, leaving researchers with an intact outer membrane or "ghost." Although other kinds of membranes can now be isolated by various

means, the mammalian red blood cell "ghost" remains the favorite subject of many scientists who work on membranes.

Studying these membranes under an electron microscope proved frustrating, however. Since electrons can pass only through ultra-thin sections, the cell was usually sliced finely with a straight knife to prepare samples for the microscope. Yet cell membranes are far from straight, and it was practically impossible to get a full-face view of a membrane in this fashion. Nor could one learn much about the membrane's inner layer.

In the early 1960's a Swiss scientist, Hans Moor, developed a method which offered an entirely new perspective on cells. Instead of chemically fixing and staining the cells, he froze them rapidly, following a technique which had previously been used in California with viruses. Then, instead of cutting the cell tissue into smooth sections, he fractured it along natural lines of weakness and bombarded the exposed surfaces with vaporized carbon and platinum, which condensed and hardened on these frozen surfaces. After he allowed the specimens to thaw out, there remained a very thin and highly detailed metal replica of the fractured plane—a replica thin enough to be viewed under an electron microscope.

Moor naturally assumed that he was looking at replicas of the cells' outer surfaces. But in fact, as Daniel Branton, who was then at the University of California, Berkeley, suggested in 1963, an extraordinary thing was happening: the membranes were being cleaved down the middle in two separate layers. "This seemed a very outrageous idea at the time, and no one believed it," recalls Branton, who is now at Harvard University. Yet there was a logical explanation for it: The two lipid layers in the center of the membrane were only weakly held together by hydrophobic interactions, and when the water froze, these interactions became irrelevant, so the membrane fell apart. By 1967 most researchers were convinced. As they began using the freeze-fracture technique to explore the

interior of membranes, they discovered little balls—protein particles—some of which were invisible from the outer surface. Furthermore, they found that the outer half of the membrane sometimes differed quite radically from the inner, cytoplasmic half, both in protein structure and in lipids. This enabled them to zero in, for the first time, on specific proteins and lipids in the center of the membrane.

While the freeze-fracture technique opened up the interior of the membrane for study, the true surface of cell membranes became visible through a special kind of electron microscope, the scanning electron microscope (SEM), which provides three-dimensional images. Unlike the transmission electron microscope, whose beams pass *through* the specimen, the SEM depends on low-energy electron beams which scan the specimen's surface, exciting secondary electrons whose pattern produces the image. Until recently, the SEM could not resolve more than 150 angstroms. "The pictures were gorgeous, but there was very little information coming out of them," recalls Palade. However, a new instrument developed in Japan is presently making it possible to see down to 30 angstroms. "So now we can start seeing the molecular details of the cell surfaces," he says. "We know that receptors in the plasma membrane must protrude from the surface of cells, but we don't know the size of these protrusions. We want to be able to obtain information about them, not only by biochemical techniques. We want to know the frequency and density of these molecules, their pattern of distribution on the cell surface, whether this distribution can be disturbed, and whether any disease states are connected with defects in it. This is the excitment about the high-resolution SEM: It brings you down to a level at which you can really *look* at molecules!"

To make full use of this instrument's power, the procedures for specimen preparation must also be refined by a factor of five. This requires new methods of "fixing" the specimens with chemicals and also new ways of spraying

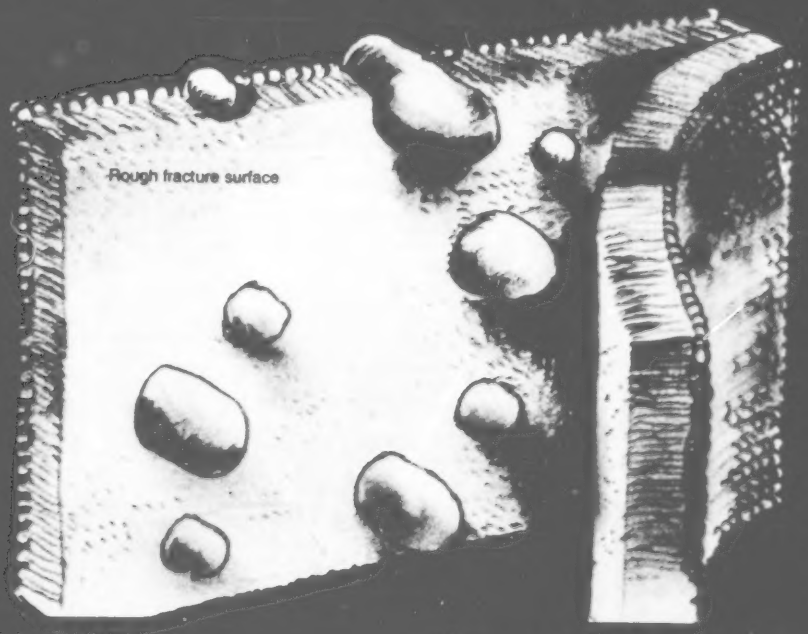
their surface with metal vapor (to make them give off secondary electrons). One advantage of working in an interdisciplinary center such as the Yale Center for Research on Cellular Membranes is that it is large enough to maintain experts who can devise such techniques. The Center consists of seven different research groups, each with its specific program and each depending, at least in part, on advanced technology in two areas: protein chemistry and the SEM. It includes some twenty-five cell biologists, biochemists, pathologists and biophysicists. "None of us uses the SEM or protein chemistry facilities full time," Palade explains, "and none of us could run these facilities with an adequate amount of attention and competence by ourselves. Here we can all use them profitably."

The Center's protein chemistry lab routinely analyzes extremely small samples of protein extracted from cell membranes. It boasts a very effective amino-acid analyzer, controlled by a computer, which uses high-pressure liquid chromatography to identify the different amino acids in a protein quickly and accurately. It also has a sophisticated machine which can determine the sequence of these amino acids from a sample of 50 micrograms or even less. Soon the Center hopes to have an additional instrument to assess the radioactivity in labelled amino-acid residues—an important tool with which to study the origins and fate of membrane proteins.

Palade's own group of 10 scientists concentrates on unraveling the "functional interaction" between cell membranes and on the membranes' genesis.

"The membranes that form compartments within cells are usually separate from one another, but some of them fuse, establishing continuity," Palade says. "This is important for secretory processes, when a cell product moves from one compartment to another and then is discharged. The membranes must know the partner with which to fuse; how do they communicate? Every time a cell divides, too, the plasma membrane fuses to split the cell, and then the two daughter cells separate. We are trying

After freeze-fracturing, a red blood cell membrane's inner layer stands revealed in this electron micrograph. The bumps are believed to represent proteins which protrude through the layer.



A model of how membranes split during freeze-fracture shows the bumps in the interior of the membrane.

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to understand this fusion-fission process. At present we only understand the recognition of a hormone or a neurotransmitter by a receptor on the plasma membrane. But we believe the same kind of thing happens *inside* the cell when membranes fuse, except that both molecules—the key and the lock—are bound to membranes. The basic principle is the same: recognition by complementarity."

Where do all these membranes come from? As Palade points out, "The cell has discovered a way to increase its membranes without disturbing their function. It appears to use always its pre-existing membranes, which behave like a fine film of olive oil, and puts new lipid and protein molecules into it, so that the film expands without ever breaking its continuity. Cells never begin making a membrane from scratch. When they divide, they give their membranes in equal parts to their daughter cells. In fact, we inherit our membranes from our mothers.

"All these membranes have their components replaced continually," he adds. "So there is a *continuity of pattern,* though not of substance. What we want to find out is where the components—the proteins and the lipids—are produced, and how they are assembled. We'd particularly like to know where the glycoproteins (sugar-bearing proteins), some of which seem to be the receptors of the plasma membrane, are synthesized.

"It's partly a matter of scientific curiosity, but there are also practical reasons: When cells have defective receptors, the actual defect may be *inside* the cell, rather than on the surface. Maybe the components are not produced in sufficient quantity. Maybe they are produced but are not transported or assembled properly. This may be relevant to cancer, as well as to questions of growth and of aging."

SEEKING A 3-D CODE FOR MEMBRANE PROTEINS

One of the Yale Center's most exciting findings so far has concerned the role of "glycophorin," a sugar-bearing protein that spans the entire thickness of the red blood cell membrane. Named by Vincent Marchesi, who succeeded in detaching it, intact, from membrane ghosts, glycophorin has some carbohydrate chains which protrude from the membrane surface like antennae and serve important functions: They act as the cell's recognition sites for blood groups and for certain viruses. In addition, they are involved in maintaining the negative charge on the cell's surface which prevents it from clumping with other red blood cells.

Glycophorin is now the best-known of the glycoproteins that extend through the cell membrane, and the first to have its amino acids completely analyzed and sequenced. Immense quantities of blood were needed to achieve this knowledge. (Twelve gallons of human blood can provide only 125 grams of membrane ghosts, which produce only 3 grams of pure protein for analysis). Just recently, Marchesi's research group made the further discovery that under certain conditions glycophorin exists in twin form, with a narrow space to separate the twin shapes, creating an open channel all the way through the membrane. Marchesi believes that these open channels are the long-sought "pores" through which materials can flow rapidly across a membrane. He also believes that glycophorin has brought him to the verge of answering several important and interrelated questions about health and disease, all of which involve the mechanism of cell-cell recognition.

For example, there is the mystery of blood platelets—billions of little bodies that float about in blood and pile up at cuts in the blood vessels to prevent the vessels from leaking. Normally these platelets do not stick to one another, but somehow, when they sense an injury to the blood vessel, their surface membranes change and they begin to clump. The mechanism involved here is very similar to that of normal cell-cell recognition, Marchesi points out. Yet in certain cases it may aggravate arteriosclerosis and other forms of cardiovascular disease.

Then there is the lure of understanding the real function of carcinoembryonic antigen (CeA), a protein found on the plasma membrane of some human tumors as well as on normal embyronic tissue. Surprisingly, CeA is an almost exact duplicate of glycophorin, differing only subtly in composition and immunological reactivity. Yet it can be used to measure the progress of certain kinds of cancer therapy: After an operation on colon cancer, for example, the level of CeA in the blood drops to almost zero, going up again if new tumors begin to grow. Researchers would like to develop other CeA-based tests which might reveal the presence of cancer very early, when it is easiest and safest to treat. This might be done through annual blood tests. However, they are hampered by "the lack of a deep enough understanding of what's going on in normal membranes," says Marchesi.

Current methods of analyzing membrane proteins are "much too simple, because what we can do is only two-dimensional," Marchesi explains. "We can see only the gross differences between molecules. But there are very subtle ways in which these little chains of peptides can fold over each other. That's the exciting part! We need to develop methods for studying these membrane proteins in three dimensions. There's an infinite amount of complex communication going on between cells, yet probably only a few molecules mediate it, like a translation system or a code. So that's the trick—to find the code. As you know, the DNA code is only four letters, in a linear arrangement. *This* code, we think, is hooked up in the 3-D

arrangement of the molecules. It's probably going to be a lot more subtle than the code for DNA."

New techniques are being developed towards this goal by Lubert Stryer, formerly of the Yale center and now at Stanford Medical School. The only proteins whose 3-D structure has been worked out by scientists so far are some 20 water-soluble proteins—for example, hemoglobin, Stryer says. Analyzing the 3-D structure of insoluble proteins, such as those in membranes, will pose a far greater challenge, he notes, since at present these proteins cannot be crystallized. Researchers in Stryer's lab are starting out with various techniques taken from physics. They are doing optical rotation experiments to see whether glycophorin has any regular structures such as a helix. They are using a Raman spectrometer, shining laser light of a known wave length onto a glycophorin sample and studying the pattern of light that it scatters as a clue to its molecular structure. They are inserting fluorescein-labelled glycophorin into an artificial membrane, to find out whether it acts as a channel for sodium and potassium, and whether altering the part of the molecule that protrudes on one side of the membrane will affect the part on the other side. They are also collaborating with the Brookhaven Laboratories in neutron studies of the molecular structure of rhodopsin, a membrane protein that is involved in vision.

"All this technology is very, very recent," says Stryer, "but it may be extremely powerful. We are building up an image of how rhodopsin sits in this membrane—it may actually go *through* the membrane. If rhodopsin turns out to be a gate that is opened by light, other gates in membranes may be opened by hormones in a similar way. That's our hope."

THE PROMISE OF NEW THERAPIES

Throughout the world, researchers who work on cell membranes realize that they have only just begun to explore a field in which anything seems possible. They share a great excitement about it.

"Can we expect to do 'membrane engineering' in the future?" S.J. Singer asked a scientific gathering recently. And he answered with a resounding, "Yes!" For example, it may be possible to change the mobility of membrane components, he says. This might have extraordinary results. Normal cells have some kind of matrix underlying their membranes which restricts the mobility of certain membrane components, he points out. Yet when cells are malignantly transformed, their membrane components can suddenly move about more easily. This on-off control of the components' mobility may well be the mechanism of growth, Singer believes; the oily film of lipids in the membrane may need to become more fluid to allow for the insertion of new molecules as the membrane grows. The same on-off control might also be a key to cancer. Scientists might then restore malignant cells to normality by providing anchoring points for the components of their plasma membranes.

Physicians already do modify the plasma membrane of their patients' cells when they use various general anesthetics, which dissolve in membrane lipids and change their properties. In the future, it is almost certain that drugs will be tailor-made to act more selectively either on proteins or on lipids in the plasma membranes of specific kinds of cells.

Some of these drugs may themselves be enclosed in ar-

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tificial membranes, forming "liposomes." In this way they could be engineered for release only when or where needed, by means of specific receptor molecules which would be inserted in the liposome membrane. "For example," suggests Cambridge University's Alec Bangham, "liposomes containing a tranquilizer could be equipped with molecules that only respond to supernormal levels of adrenalin." Similarly, liposomes loaded with antitumor agents could be keyed to the properties of specific tumor cells so that the drug would be released only when the liposome came in actual contact with the malignant cell. "By this method," Bangham explains, "It would be possible to employ drugs far too toxic for administration through the general circulation." Experiments of this sort are already under way in Christian de Duve's lab and in other places.

Other researchers have been working on ways to correct the intricate feedback system through which cells control the production of such vital chemicals as cholesterol, in cases when the system fails. As Joseph Goldstein and Michael Brown of the University of Texas discovered recently, each person's production of cholesterol is controlled by the activity of specific receptors for LDL (low-density lipoproteins, the particles which carry cholesterol in the blood) in his or her cells' plasma membranes—and these receptors in turn increase or decrease according to the amount of cholesterol in the cell. [Mammalian cells can both produce their own cholesterol and take up cholesterol from the blood. When a normal cell needs more cholesterol than it has produced, it synthesizes more LDL receptors. These transmit LDL from the blood to the cytoplasm, where lysosomes break it down, releasing cholesterol. As soon as the cholesterol in the cytoplasm reaches a certain concentration, however, it shuts off the enzyme that produces cholesterol inside the cell—and also stops the synthesis of additional LDL receptors.]

The system works pretty much like a thermostat to ensure that the cell always has enough cholesterol for life and growth, without accumulating too much of it. Because of a defective gene, however, some people do not have a sufficient number of LDL receptors in their cells. This is what happens in familial hypercholesterolemia, where the lack of LDL receptors breaks the normal chain of control and leads to overproduction of cholesterol. Among people who suffer heart attacks before the age of 60, one out of 20 have been found to carry this defective gene (which actually occurs in about one out of 500 persons in the general population). Now that scientists understand the feedback system involved, they realize why existing anticholesterol drugs are so often ineffective: lowering the amount of cholesterol in the blood may actually lead the flawed cells to produce even more of it, to make up for the loss. By contrast, new drugs which are now being tested would specifically reduce the cell's ability to make cholesterol, rather than remove more of the cholesterol that is already made.

Many forms of mental illness may also turn out to be related to defects in specific proteins that act as receptors for hormones and neurotransmitters on the plasma membrane. If so, it may be possible to develop far more effective drugs which would take account of the cell's feedback systems.

Every new bit of information about the inner workings of the cell leads towards the development of better weapons against the diseases that still plague us. As researchers learn more about membranes, for example, they are indirectly contributing to the prevention or cure of such seemingly unrelated ailments as diabetes, heart disease, various genetic defects, cancer, and even kidney disease, for the kidney is composed largely of membranes. New vaccines and new immunologic weapons also await a better understanding of the cell and its organelles.

While today's physicians view diseases in terms of

organs, such as liver diseases, bone diseases or heart diseases, the physicians of the next generation will see these ailments as diseases of cell membranes and organelles—for example, diseases of the endoplasmic reticulum, lysosomal diseases, or mitochondrial diseases. Thus, heart disease will be examined not simply in terms of which chamber and portion of the heart is involved, as determined by the EKG, but in terms of the specific lesion within the heart muscle cells that leads to malfunction and cell death.

This has been a period of "spectacular growth" in cell biology, the President's Biomedical Research Panel declared recently. "Basic biological and biomedical sciences have progressed faster over the last 25 years than at any time during their long history... For the first time in the history of the life sciences, the essential function of cells can be understood in terms of defined chemical reactions." Yet despite all this progress, most of medicine is still far from being a true science.

The reason for this gap is that, until now, scientists could not even study the mechanisms which regulate such basic processes as cell growth, division, or mobility; they simply did not have enough information about the cell's components. They are barely starting to understand how cells are controlled. But now the stage is set. A far more powerful type of research on the cellular and molecular basis of disease can begin. And as it builds up a clearer picture of normal and abnormal cell function, it will create a truly scientific medicine for the 21st century.

GLOSSARY

amino acid—a building block of protein. Twenty different amino acids are commonly found in cells as the constituents of proteins.

angstrom—a unit of length, one hundred-millionth of a centimeter (approximately .000000004 inches); commonly used for describing atomic dimensions.

antibody—a protein produced by the body in response to a foreign substance (antigen), to render it harmless.

ATP (adenosine triphosphate)—the compound which serves as a source of energy for physiological reactions in all living cells.

carbohydrate—a class of compounds related to the sugars, such as glucose, starch or cellulose.

cell—the basic sub-unit of any living system; the simplest unit that can exist as an independent living system.

chromosome—a structure found in the cell nucleus and containing the genes. Chromosomes are composed of DNA and proteins. They can be seen in the light microscope during some stages (but not others) of cell division.

culture—the propagation of cells or tissues in special nutrients, conducive to their growth.

cytoplasm—all the substance of a cell, excluding the nucleus.

differentiation—the series of biochemical and structural changes that groups of cells undergo in order to form a specialized tissue.

DNA (deoxyribonucleic acid)—the substance of heredity; a large molecule which carries the genetic information necessary for the replication of cells and which directs the building of proteins.

electron microscope—a powerful microscope which uses beams of high-speed electrons instead of light waves.

endocytosis—the uptake of protein and other molecules from outside the cell by the plasma membrane, which folds in to envelop them, forming small vesicles which move into the cytoplasm.

enzyme—a protein substance which speeds up, or catalyzes, the chemical reactions of a cell.

ER (endoplasmic reticulum)—an organelle made up of membranes, forming a system of tubes and flattened sacs continuous with the nuclear membrane. Some of these membranes are smooth (the SER) and others are "rough" (the RER), dotted with ribosomes.

eucaryotic cell—a cell that has a true nucleus (from the Greek "karyon" for "kernel") with a membrane around it. The cells of all animals and plants, except blue-green algae, fall in this category.

exocytosis—the movement of substances that are packaged in membranous envelopes towards the cell's surface, where the envelopes fuse with the plasma membrane and release their contents outside the cell.

gene—a unit of heredity; a segment of the DNA molecule containing the code for a particular protein, and thus for a detectable function.

genetic code—the language in which DNA's instructions are written; it consists of triplets of nucleotides with each triplet corresponding to one amino acid.

glycoprotein—a protein with an attached carbohydrate group.

Golgi apparatus (or Golgi complex)—a system of membranous sacs in the cell which packages molecules into capsules and sends them on their way to the cell's surface.

hormone—a chemical substance made in one part of the body and transported, via the bloodstream, to another part, where it has a marked effect.

interference microscope—a light microscope which measures the refractive index of microscopic objects, including parts of living cells. It is similar to the phase-contrast microscope, but also provides a guide to dry mass or thickness.

lipoproteins—compounds of fatty substances (lipids) and proteins; some of the lipoproteins in blood carry cholesterol.

liposome—artificial bubble made up of lipids and containing substances designed to be absorbed by specific cells.

lysosome—small organelle containing powerful enzymes which are capable of digesting a variety of materials.

membrane—a complex film of lipids interspersed with proteins which covers the cell and many organelles, controlling what goes in and what comes out, and also makes up other organelles, such as the ER.

microfilaments—thread-like organelles involved in cell motion.

micrometer (or micron)—one-thousandth of a millimeter; 10,000 angstroms; convenient for describing the dimensions of cells and organelles.

microtubules—thin tubular organelles which act as the cell's physical props.

mitochondria—organelles which act as the cell's power plants, converting the energy in carbohydrates to ATP.

neuron—a nerve cell, unit of the nervous system.

neurotransmitter—a chemical messenger released by one nerve cell which affects the permeability of the membrane of an adjacent cell, such as a neuron or muscle cell.

nucleic acid—any of two kinds of acids that carry genetic information, DNA and RNA, formed by chains of nucleotides.

nucleolus—a densely packed region in the nucleus, where ribosomal RNA is made.

nucleotide—a building block of DNA or RNA; two nucleotides, fitted together according to their chemical bases, make up each rung in the ladder of the DNA molecule.

nucleus—the biggest structure in the cell, containing the chromosomes.

organelle—a specialized structure having a definite function in a cell; for example, the nucleus, a mitochondrion, a ribosome.

peptide—a string of amino acids joined by covalent bonds.

phagocytic cells—scavenger cells which engulf and destroy microorganisms and other foreign particles that invade the body.

phase-contrast microscope—a light microscope which uses the differences in refractive index between organelles and their surrounding cytoplasm to obtain contrast. Thus, organelles can be seen without staining and their size, shape and motion can be observed in the living state.

plasma membrane—the surface membrane of cells, containing protein and lipids, which directs traffic in and out of the cell.

procaryotic cell—a cell which does not have any membrane around its nuclear region; for example, a bacterium.

protein—a molecule made up from a number of different amino acids arranged in a special order determined by the genetic code; proteins are required for all life processes.

recombinant DNA technology—techniques for cutting apart and splicing together pieces of DNA from different organisms. When segments of human or

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animal DNA are transferred into another organism, such as a bacterium, these segments replicate and may be expressed together with the bacterium's own genetic material.

ribosomes—organelles which contain RNA and protein, and are the sites of protein synthesis.

RNA (ribonucleic acid)—a nucleic acid which plays an important role in transmitting and translating the genes' instructions to the cytoplasm; it also forms the genetic material of certain viruses.

ultracentrifuge—a powerful centrifuge, similar in principle to a cream separator. It is used to separate many of the smaller and lighter components of the cell.

X-ray crystallography—a technique for studying the 3-D structure of molecules through the mathematical analysis of their X-ray diffraction patterns.

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